BMJ Neurology Open

RE-OPEN: Randomised trial of biosimilar TNK versus TPA during endovascular therapy for acute ischaemic stroke due to large vessel occlusions

Rohit Bhatia ,[1] MV Padma Srivastava,[1] Saman Fatima,[1] Risha Sarkar,[1] Imnameren Longkumer,[1] Shailesh Gaikwad,[2] Leve S Joseph Devaranjan,[2] Ajay Garg,[2] Jeyaraj Durai Pandian,[3] Dheeraj Khurana,[4] PN Sylaja,[5] Shweta Jain,[3] Deepti Arora,[3] Aneesh Dhasan,[5] Sanjith Aaron,[6] Angel T Miraclin,[6] Pamidimukkala Vijaya,[7] Srijithesh P Rajendran,[8] Jayanta Roy,[9] Biman Kanti Ray,[10] Vivek Nambiar,[11] Paul J Alapatt,[12] Meenakshi Sharma,[13] on behalf of RE-OPEN Trial Collaborators

To cite: Bhatia R, Srivastava MVP, Fatima S, *et al*. RE-OPEN: Randomised trial of biosimilar TNK versus TPA during endovascular therapy for acute ischaemic stroke due to large vessel occlusions. *BMJ Neurology Open* 2024;**6**:e000531. doi:10.1136/bmjno-2023-000531

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjno-2023-000531).

Received 09 September 2023
Accepted 08 October 2023

For numbered affiliations see end of article.

Correspondence to
Dr Rohit Bhatia;
rohitbhatia71@yahoo.com

ABSTRACT

Rationale Rapid and timely treatment with intravenous thrombolysis and endovascular treatment (EVT) in patients with acute ischaemic stroke (AIS) and large vessel occlusion (LVO) significantly improves patient outcomes. Bridging therapy is the current standard of care in these patients. However, an incompletely answered question is whether one thrombolytic agent is better than another during bridging therapy.

Aim The current study aims to understand if one thrombolytic agent is superior to the other during bridging therapy in the treatment of AIS and LVO.

Sample size estimates Using 80% power and an alpha error of 5 %, presuming a 10% drop out rate, a total of 372 patients will be recruited for the study.

Methods and design This study is a prospective, randomised, multicentre, open-label trial with blinded outcome analysis design.

Study outcomes The *primary outcomes* include proportion of patients who will be independent at 3 months (modified Rankin score (mRS) ≤2 as good outcome) and proportion of patients who achieve recanalisation modified thrombolysis in cerebral infarction grade 2b/3 at first angiography run at the end of EVT. *Secondary outcomes* include proportion of patients with early neurological improvement, rate of symptomatic intracerebral haemorrhage (ICH), rate of any ICH, rate of any systemic major or minor bleeding and duration of hospital stay. *Safety outcomes* include any intracranial bleeding or symptomatic ICH.

Discussion This trial is envisioned to confirm the theoretical advantages and increase the strength and quality of evidence for use of tenecteplase (TNK) in practice. Also, it will help to generate data on the efficacy and safety of biosimilar TNK.

Trial registration number CTRI/2022/01/039473.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Bridging therapy with endovascular thrombectomy preceded by intravenous thrombolysis is currently accepted as a standard of care in acute ischaemic stroke (AIS) caused by large vessel occlusions (LVO). However, there is an uncertainty if tenecteplase (TNK) is superior to alteplase (rTPA) as a thrombolytic agent among patients with LVO.

WHAT THIS STUDY ADDS

⇒ This is an ongoing trial comparing the efficacy of biosimilar TNK with rTPA for bridging therapy. It will provide class I evidence about the choice of thrombolytic agent in patients with AIS due to LVO, as well as the efficacy and safety of biosimilar TNK.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ If the trial demonstrates superiority of intravenous TNK when compared with rTPA among patients with AIS due to LVO, it may change clinical practice and potentially improve ease of treatment and reduce the cost of therapy.

INTRODUCTION AND RATIONALE

Recent times have observed major trials of bridging therapy with endovascular thrombectomy preceded by intravenous thrombolysis, most of whom have been conducted with recombinant tissue plasminogen activator (rTPA).[1]

There has been a debate if tenecteplase (TNK) is superior to rTPA as a thrombolytic agent. Some metanalyses reported recently suggest that TNK is non-inferior to TPA but superiority is not certain.[1–3] Since TNK is thought to be potentially superior for cost,

feasibility, treatment effect and recanalisation rates, it may be prudent to study the benefit of one thrombolytic agent over the other. The EXTEND IA TNK study observed that 22% of patients in the TNK arm versus 10% of patients in the alteplase arm had substantial reperfusion on the initial angiogram (*P* for non-inferiority=0.002; *P* for superiority=0.02), with a risk difference of 12% and an adjusted OR of 2.6 (95% CI 1.1 to 5.9). After adjustment for age and baseline National Institutes of Health Stroke Scale (NIHSS) score, a shift toward less disability (ordinal common OR=1.7; 95% CI 1 to 2.8) with TNK was also demonstrated. The results suggested that use of TNK was associated with higher recanalisation compared with rTPA and better outcomes on both dichotomised as well as ordinal analysis of the modified Rankin score (mRS).[4] The follow-up study, EXTEND IA TNK part 2, observed no additional benefit of using 0.4 mg/kg dose of TNK compared with 0.25 mg/kg.[5] This study will provide evidence for use of TNK as bridging therapy, as well as the efficacy and safety of biosimilar TNK in 4.5 hours among patients with acute ischaemic stroke (AIS) and large vessel occlusion (LVO).

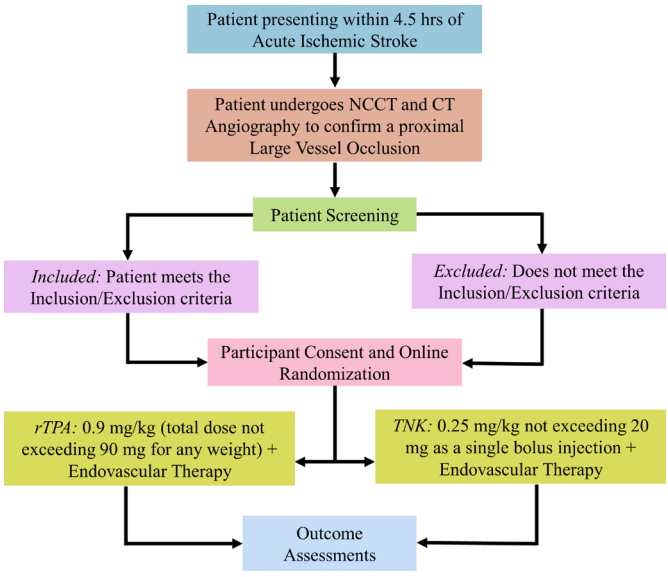

Figure 1 Study workflow of the RE-OPEN trial. RE-OPEN, Randomised trial of biosimilar TNK versus TPA during endovascular therapy for acute ischaemic stroke due to large vessel occlusions; NCCT, non-contrast CT.

METHODS

Study design

This is a prospective, randomised, multicentre, open-label trial with blinded outcome analysis design. The trial started in September 2022, and is expected to be completed by August 2025, corresponding to a total duration of 36 months. There are 12 study sites across the country which are part of the Indian Stroke Clinical Trial Network (INSTRuCT) collaborative sites.[6] The protocol has been written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. The trial is registered with the Clinical Trial Registry of India with reference number: CTRI/2022/01/039473. The study flow is outlined in figure 1.

Patient population

All patients with a diagnosis of acute stroke, presenting to the emergency within 4.5 hours of the onset will be screened for eligibility. All patients will undergo a rapid history review, non-contrast CT (NCCT) and multiphasic CT Angiogram (CTA) for defined inclusion and exclusion criteria. In case the treating neurologist decides to treat the patient based on his/her judgement out of the criteria laid for this trial, the patient will not be randomised into the study.

Inclusion criteria

1. Age ≥18 years.
2. Patients with AIS.
3. Within 4.5 hours of onset of stroke.
4. NIHSS (≥ 5).
5. Presence of a proximal large vessel occlusion (Distal Internal Carotid artery (ICA), M1 Middle Cerebral artery (MCA), proximal M2 MCA, Basilar artery) on CTA/MRA.
6. Alberta Stroke Program Early CT score (ASPECTS score) ≥6
7. Eligible for thrombolysis as per standard inclusion and exclusion criteria.
8. Eligible for endovascular treatment (EVT) as per the current guidelines.
9. EVT (groin puncture) can begin within 6 hours of stroke onset.
10. Agrees for endovascular therapy as a part of standard treatment for LVO.
11. Informed and signed consent.

Exclusion criteria

1. Patients with intracerebral haemorrhage (ICH).
2. Hypodensity in >1/3 rd of MCA territory.
3. Recent ischaemic stroke within 3 months.
4. ASPECTS less than 6.
5. Recent history of ICH, subarachnoid haemorrhage, arteriovenous malformation, aneurysm or cerebral neoplasm.
6. Current use of vitamin K antagonist (VKA) with international normalised ratio (INR)≥1.7.
7. Non-availability of INR if patient is on VKA.
8. Current use of novel oral anticoagulants.
9. Active use of heparin in therapeutic doses.
10. Use of glycoprotein IIb-IIIa inhibitors within the past 72 hours.
11. Clinically significant hypoglycaemia.
12. Persistently elevated blood pressure greater than 185 mmHg systolic and 110 mmHg diastolic.
13. Hereditary or acquired haemorrhagic diathesis.
14. Gastrointestinal or urinary bleeding within the preceding 21 days.

15. Major surgery within the preceding 14 days.
16. Any cranial or spinal surgery within 3 months.
17. Baseline mRS ≥2.
18. Active pregnancy.
19. Contraindication to contrast agents.
20. Intracardiac tumour.
21. Active subacute bacterial endocarditis.
22. 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.

Randomisation

Following an informed written consent, all patients who had a consecutive acute ischaemic stroke with an LVO meeting criteria for intravenous thrombolysis followed by endovascular therapy will undergo 1:1 randomisation by computer-generated permuted block randomisation and allocation to either intravenous rTPA or TNK prior to the EVT procedure.

Allocation and concealment

The allocation will be made in real time through the centralised web-based randomisation with a unique code assigned to each randomised patient.

Blinding

This will be an open-label trial. However, all personnel involved in the subsequent clinical and imaging assessment of outcomes will be blinded to the treatment allocation.

Data shall be collected in a predefined proforma on an anonymised online data collection platform. Details of demographic data, baseline risk factors, stroke metrics and complications shall be closely monitored and recorded.

Treatment or intervention

Thrombolysis

All eligible patients will be randomly assigned to receive intravenous thrombolysis with one of the following intravenous thrombolytic agents.

1. Recombinant tissue plasminogen activator (rTPA, Actilyse, Boehringer Ingelheim): 0.9 mg/kg (total dose not exceeding 90 mg for any weight). Ten per cent of the dose shall be given as bolus and the remaining as an infusion over 1 hour.

2. Tenecteplase (TNK, Gennova Pharmaceuticals): 0.25 mg/kg not exceeding 20 mg as a single bolus injection.

All eligible patients will be transferred to the angiography suite for EVT with either a stent retriever (preferably) or an aspiration device (Penumbra), or both, whichever the interventionist feels justified for use. Details of recanalisation achieved as measured using modified thrombolysis in cerebral infarction (mTICI) classification grade will be recorded.[7] Patients will be transferred to the in-hospital stroke unit for strict monitoring after the procedure.

Monitoring

All patients will be closely monitored for any complication during or after the procedure. NIHSS will be recorded immediately after the procedure and thereafter every 6 hours for the next 72 hours and at the time of discharge. NCCT head will be repeated at 24 hours in all patients to observe any bleeding and also estimate the ASPECTS score. Repeat NCCT shall be done after 24 hours if dictated by the clinical course. For any ICH or systemic bleeding, details will be recorded for drop in NIHSS, sensorium, haemoglobin and need for blood transfusion, fresh frozen plasma, cryoprecipitate or any surgical intervention. Any adverse event shall be closely monitored, recorded and appropriately managed.

Follow-up

Patients will be followed up after discharge at 1 and 3 months for study outcomes and thereafter in the neurology/stroke clinics for standard follow-up. Three months outcome shall be recorded by a blinded assessor either in person or on phone for mRS. Any mortality will be recorded and a verbal autopsy will be done to establish the likely cause.

Outcomes

Primary outcomes

1. Proportion of patients who will be independent at 3 months (using mRS ≤2 taken as a good outcome)
2. Proportion of patients who achieve recanalisation mTICI grade 2b/3 at first angiography run and at the end of the EVT procedure.

Secondary outcomes

1. Proportion of patients with early neurological improvement defined as improvement of NIHSS by four points at 24 hours.
2. Rate of symptomatic ICH as defined using safe implementation of thrombolysis in stroke monitoring study (SITS MOST) criteria.[8]
3. Rate of any ICH.
4. Rate of any systemic major or minor bleeding using Global Use of Streptokinase and tPA for occluded Coronary Arteries (GUSTO) classification.[9]
5. Duration of hospital stay.

Safety outcomes

1. Any intracranial bleeding or symptomatic ICH.

Data safety monitoring body

The data safety monitoring body (DSMB) is constituted with independent members from within and outside the country for all the ongoing trials in the INTRuCT Network, who are not a part of any trial. The DSMB shall meet periodically every 6 to 12 months to assess trial workflow and any adverse events related to the safety of the trial and recommend its continuation or withdrawal.

Image adjudication committee

All imaging including baseline CT/MRI scan/CTA/MRA and angiographic images during the EVT procedure will be uploaded into a web-based server in digital imaging and communications in medicine format by all sites. An image adjudication committee constituted by neuroradiologists will centrally adjudicate all patient imaging.

Sample size estimates

In the EXTEND IA-TNK trial, 64% patients in the TNK arm versus 51% patients in the TPA arm achieved a good outcome (mRS 2 or below) suggesting an absolute benefit of 13% with TNK.[4] However, the patients in this study were selected initially on the basis of predefined mismatch on CT Perfusion. Later, even higher core volumes were selected. We propose an estimate of 15% increase in good outcome in the TNK group based on the results above. Using 80% power and an alpha error of 5%, 169 patients are required in each group. Presuming a 10% drop out rate, an estimated 186 patients are required in each group. Therefore, a total of 372 patients will be recruited for the study.

Statistical analyses

Statistical analyses will be done using STATA updated version. The qualitative variables will be assessed using the χ^2 test. Mean±SD will be used for quantitative variables and Student's t-test shall be used for bivariate analysis. Where data are skewed, median IQR and Wilcoxon sum rank shall be used to estimate results. Outcomes shall be dichotomised into good and bad outcome at mRS 2 or below. Ordinal analysis with mRS shall also be performed and a common OR shall be observed for significance of results. A two-tailed p value of <0.05 will be taken as significant.

DISCUSSION

Bridging therapy is currently the standard of care among eligible patients with AIS and LVO.[10 11] Majority of the AIS guidelines recommend the use of rTPA as a standard agent for bridging therapy as most trials in the past have used rTPA.

It is prudent to study newer bridging agents which have a higher chance of recanalisation, can be given rapidly and also have an economic benefit. There has been a growing interest in the use of TNK. TNK is thought to be potentially superior for cost, feasibility, treatment effect and recanalisation rates. The results of EXTEND IA TNK suggested that the use of TNK was associated with higher recanalisation compared with TPA and better outcomes on both dichotomised as well as ordinal analysis of the mRS.[4] Recently, many trials comparing TNK to rTPA have been published suggesting non-inferiority of TNK in the management of AIS within 4.5 hours. A few metanalyses suggested that TNK is non-inferior to TPA but superiority is uncertain.[1–3] The recently conducted AcT (intravenous TNK compared with alteplase for acute ischaemic stroke in Canada) trial showed that TNK was non-inferior to alteplase for patients presenting with AIS meeting standard indications for thrombolysis.[12] Recently, published trials have compared direct EVT to bridging therapy for LVO management with no definitive evidence of superiority. These trials have used alteplase and no comparison to TNK is available.[11]

The present trial will confirm the theoretical advantages of TNK and increase the strength of evidence for its use in practice during bridging therapy. The study will enrol patients based on a simple paradigm of NCCT and CTA and therefore will be easy to reproduce in clinical practice, where imaging based strict selection using perfusion-based imaging is not practical and pragmatic. This will be a pragmatically driven, practically applicable and easy to perform trial. The trial will use a centralised randomisation process using real-time web-based servers for randomisation and drug allocation. The use of blinded assessors to assess 90-day primary and secondary outcomes will help limit bias and provide a real-world assessment of efficacy and safety.

SUMMARY AND CONCLUSIONS

Results from the RE-OPEN trial will provide class I evidence about the choice of thrombolytic agent in patients with AIS and LVO as well as the effectiveness of intravenous biosimilar TNK in patients with acute ischaemic stroke eligible for intravenous thrombolysis. If the trial demonstrates superiority of intravenous TNK when compared with alteplase, it will strengthen the existing evidence and may lead to a change in clinical practice.

Author affiliations
[1]Department of Neurology, All India Institute of Medical Sciences, New Delhi, India
[2]Department of Neuroimaging and Interventional Neuroradiology, All India Institute of Medical Sciences, New Delhi, India
[3]Department of Neurology, Christian Medical College, Ludhiana, India
[4]Department of Neurology, Post Graduate Institute of Medical Education & Research, Chandigarh, India
[5]Department of Neurology, Sree Chitra Tirunal Institute of Medical Sciences & Technology, Thiruvananthapuram, India
[6]Department of Neurology, Christian Medical College, Vellore, India
[7]Department of Neurology, Lalitha Superspeciality Hospital, Guntur, India
[8]Department of Neurology, National Institute of Mental Health and Neurosciences, Bangalore, India
[9]Department of Neurology, Institute of Neurosciences, Kolkata, India
[10]Department of Neurology, Bangur Institute of Neurosciences and IPGMER, Kolkata, India
[11]Department of Neurology, Amrita Institute of Medical Sciences, Kochi, India
[12]Department of Neurology, Aster MIMS, Calicut, India
[13]Indian Council of Medical Research, New Delhi, India

Acknowledgements We thank members of the ICMR Task Force Committee of the INSTRuCT Network for their valuable advise.

Collaborators The RE-OPEN Trial Collaborators includes: Awadh K Pandit (All India Institute of Medical Sciences, New Delhi), Deepti Vibha (All India Institute of Medical Sciences, New Delhi), Venugopalan Y Vishnu (All India Institute of Medical Sciences, New Delhi), Rajesh Kumar Singh (All India Institute of Medical Sciences, New Delhi), Ayush Agarwal (All India Institute of Medical Sciences, New Delhi), Rajeshwar Sahonta (Christian Medical College, Ludhiana), Rahul Huilgol (Christian Medical College, Ludhiana), Arya Devi KS (Christian Medical College, Ludhiana), Chirag Ahuja (Post Graduate Institute of Medical Education &

Research, Chandigarh), Pheba Susan Raju (Sree Chitra Tirunal Institute of Medical Sciences and Technology, Thiruvananthapuram), ER Jayadevan (Sree Chitra Tirunal Institute of Medical Sciences and Technology, Thiruvananthapuram), Sapna Erat Sreedharan (Sree Chitra Tirunal Institute of Medical Sciences and Technology, Thiruvananthapuram), Santhosh Kumar K (Sree Chitra Tirunal Institute of Medical Sciences and Technology, Thiruvananthapuram), Sajith K (Sree Chitra Tirunal Institute of Medical Sciences and Technology, Thiruvananthapuram), Abdurehiman KP (Aster MIMS, Calicut), Sreevidya LK (Aster MIMS, Calicut), Deep Das (Bangur Institute of Neurosciences and IPGMER, Kolkata), Subhadeep Banerjee (Institute of Neurosciences, Kolkata), Srinivas Reddy (Lalitha Superspeciality Hospital, Guntur), Pritam Raja (National Institute of Mental Health and Neurosciences, Bangalore), Girish Baburao Kulkarni (National Institute of Mental Health and Neurosciences, Bangalore), RS Dhaliwal (Indian Council of Medical Research, New Delhi).

Contributors RB conceptualised and designed the study. MVPS, SG, LSJD, AG, JDP, DK, PNS, SA, ATM, PV, SPR, JR, BKR, VM, PJA and MS contributed to the description of the study design. SF, RS, IL, SJ, DA and AD are the trial core clinical coordinators pan-India and contributed to development of the study workflow. RB and SF drafted the manuscript. All authors critically revised the manuscript and approved the final version before submission. All authors had full access to the final manuscript and had final responsibility for the decision to submit for publication

Funding The study has been funded by the Indian Council of Medical Research (ICMR) (reference number: SWG/Neuro/43/TF Centre I/2020-NCD-I).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Institute Ethics Committee, All India Institute of Medical Sciences (IEC-172/11.04.2020, RP-38/2021). Participants will be enrolled in the study after informed consent.

Provenance and peer review Not commissioned; internally peer reviewed.

ORCID iD

Rohit Bhatia http://orcid.org/0000-0001-7662-3202

REFERENCES

1 Huang X, MacIsaac R, Thompson JL, *et al*. Tenecteplase versus alteplase in stroke thrombolysis: an individual patient data meta-analysis of randomized controlled trials. *Int J Stroke* 2016;11:534–43.
2 Thelengana A, Radhakrishnan DM, Prasad M, *et al*. Tenecteplase versus alteplase in acute ischemic stroke: systematic review and meta-analysis. *Acta Neurol Belg* 2019;119:359–67.
3 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.
4 Campbell BCV, Mitchell PJ, Churilov L, *et al*. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *N Engl J Med* 2018;378:1573–82.
5 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.
6 Pandian JD, Verma SJ, Arora D, *et al*. Instruct: protocol, infrastructure, and governance. *Stroke* 2021;52:e574–80.
7 Tung EL, McTaggart RA, Baird GL, *et al*. Rethinking thrombolysis in cerebral infarction 2B: which thrombolysis in cerebral infarction scales best define near complete recanalization in the modern thrombectomy era *Stroke* 2017;48:2488–93.
8 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.
9 Selby JV, Friedman GD, Quesenberry CP, *et al*. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med* 1992;326:653–7.
10 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.
11 Du H, Lei H, Ambler G, *et al*. Intravenous thrombolysis before mechanical thrombectomy for acute ischemic stroke: a meta-analysis. *J Am Heart Assoc* 2021;10:e022303.
12 Menon BK, Buck BH, Singh N, *et al*. Intravenous tenecteplase compared with Alteplase for acute ischaemic stroke in Canada (act): a pragmatic, multicentre, open-label, Registry-linked, randomised, controlled, non-inferiority trial. *Lancet* 2022;400:161–9.