Clinical trial results:
Multi-Centre, prosepective randomised open label, blinded-endpoint (PROBE) controlled trial of thrombolysis with low dose Tenecteplase (TNK-tPA) versus standard of care in the prevention of disability at 3 months in minor ischemic stroke with proven acute symptomatic occlusion.

Summary

EudraCT number	2015-005469-22
Trial protocol	AT IE ES FI
Global end of trial date	19 January 2024

Results information

Result version number	v1 (current)
This version publication date	01 February 2025
First version publication date	01 February 2025
Summary attachment (see zip file)	The Lancet TEMPO 2 2024 (rct TEMPO2 2024 (1).pdf)

Trial information

Trial identification

Sponsor protocol code	TEMPO-2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02398656
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Calgary
Sponsor organisation address	2500 University Drive, Calgary, Canada, AB T2N 2T9
Public contact	Dr Shelagh B. Coutts, University of Calgary, 1 4039441594, scoutts@ucalgary.ca
Scientific contact	Dr Shelagh B. Coutts, University of Calgary, 1 4039441594, scoutts@ucalgary.ca

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 January 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 January 2024
Global end of trial reached?	Yes
Global end of trial date	19 January 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective: to demonstrate the efficacy of using TNK--tPA to treat minor ischemic stroke with proven arterial occlusion.

Protection of trial subjects:

Follow up at 90 days

Background therapy:

Individuals with minor ischaemic stroke and intracranial occlusion are at increased risk of poor outcomes.
Intravenous thrombolysis with tenecteplase might improve outcomes in this population. We aimed to test the
superiority of intravenous tenecteplase over non-thrombolytic standard of care in patients with minor ischaemic
stroke and intracranial occlusion or focal perfusion abnormality.

Evidence for comparator: -

Actual start date of recruitment	01 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 514
Country: Number of subjects enrolled	Australia: 168
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	Brazil: 19
Country: Number of subjects enrolled	Spain: 64
Country: Number of subjects enrolled	United Kingdom: 83
Country: Number of subjects enrolled	Austria: 20
Country: Number of subjects enrolled	Finland: 13
Country: Number of subjects enrolled	Ireland: 3
Worldwide total number of subjects	886
EEA total number of subjects	100

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	281
From 65 to 84 years	489
85 years and over	116

Subject disposition

Recruitment

Recruitment details:

Eligible patients with minor acute ischaemic stroke and intracranial occlusion or focal perfusion abnormality were enrolled within 12 h from stroke onset. Participants were randomly assigned (1:1), using a minimal sufficient balance algorithm to intravenous tenecteplase (0·25 mg/kg) or non-thrombolytic standard of care (control).

Pre-assignment

Screening details:

The principles of patient selectionare based upon the broad criteria of:
a. TIAor minor stroke presentation with a diagnosis of an ischemic stroke syndrome
b. Imaging proof of an intracranial occlusion or a perfusion abnormality relevant to the presenting symptoms
c. No region of well-defined hypodensity on the NCCT

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

Blinding was ensured to allocation of the treatment by the outcome assessment and not sites involved by having at the 90 days a person who conduct was blinded during the acute treatment period

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention Arm

Arm description:

In the intervention group TNK-tPA is given as a single, intravenous bolus immediately upon randomization. Maximum dose (0.25mg/Kg) 50mg.

Arm type	Experimental
Investigational medicinal product name	Tenecteplase
Investigational medicinal product code	
Other name	TNK-tPA
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

TNK-tPA(0.25mg/kg) given as a single, intravenous bolus immediately upon randomization. Experimental treatment will be administered as a single intravenous bolus over 5-10 seconds as per the standardmanufacturers' instructions for use.

Arm title	Control Arm

Arm description:

Patients will be treated with standardof care based antiplatelet treatment

Arm type	No intervention

No investigational medicinal product assigned in this arm

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Blinding of the outcome assessment at 90 days will be ensured at the site by having a person who was blinded to treatment allocation and not involved in the acute treatment period conduct the assessment.

This is a per the Protocol

Number of subjects in period 1[2]	Intervention Arm	Control Arm
Started	432	454
Completed	425	442
Not completed	7	12
Consent withdrawn by subject	-	2
Transferred to other arm/group	1	4
Lost to follow-up	-	2
Protocol deviation	6	4

Notes:

[2] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.
Justification: 4 pts from the control arm crossed over to thrombolysis and were given intravenous alteplase

1 pt from the treatment arm crossed over to the control arm and was given aspirin plus clopidogrel

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description:

The primary outcome occurred in 338 (75%) of 452 patients in the control group and 309 (72%) of 432 in the tenecteplase group (risk ratio [RR] 0·96, 95% CI 0·88–1·04, p=0·29). More patients died in the tenecteplase
group (20 deaths [5%]) than in the control group (five deaths [1%]; adjusted hazard ratio 3·8; 95% CI 1·4–10·2,
p=0·0085). There were eight (2%) symptomatic intracranial haemorrhages in the tenecteplase group versus two (<1%)
in the control group (RR 4·2; 95% CI 0·9–19·7, p=0·059).

Reporting group values	Overall Trial	Total	
Number of subjects	886	886	
Age categorical			
adult patients (aged ≥18 years) were included			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	281	281	
From 65-84 years	489	489	
85 years and over	116	116	
Age continuous			
adult patients (aged ≥18 years)			
Units: years			
arithmetic mean	72		
standard deviation	± 0	-	
Gender categorical			
886 patients were enrolled; 369 (42%) were female and 517 (58%) were male			
Units: Subjects			
Female	369	369	
Male	517	517	

End points

End points reporting groups

Reporting group title	Intervention Arm
Reporting group description:	
In the intervention group TNK-tPA is given as a single, intravenous bolus (0.25mg/Kg) immediately upon randomization. Maximum dose 50mg.	
Reporting group title	Control Arm
Reporting group description:	
Patients will be treated with standardof care based antiplatelet treatment	

Primary: Return to baseline neurological functioning as measured by the mRS

End point title	Return to baseline neurological functioning as measured by the mRS[1]

End point description:

Primary outcome: Return to baseline neurological functioning as measured by the mRS.

Analysis will be a responder analysis where return to baseline level of neurological functioning using a variation of the sliding dichotomy modified Rankin Scale score outcome, defined as follows:
If pre-morbid mRS is 0-1 then mRS 0-1 at 90 days is a good outcome.
If pre-morbid mRS is 2 then mRS 0-2 is a good outcome.

Pre-morbid mRS is assessed using the structured mRS prior to randomization.

End point type	Primary

End point timeframe:

90 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Primary outcome: Return to baseline neurological functioning as measured by the mRS. Analysis will be a responder analysis where return to baseline level of neurological functioning using a variation of the sliding dichotomy modified Rankin Scale score outcome, defined as follows:
If pre-morbid mRS is 0-1 then mRS 0-1 at 90 days is a good outcome.
If pre-morbid mRS is 2 then mRS 0-2 is a good outcome.
Pre-morbid mRS is assessed using the structured mRS prior to randomization.

End point values	Intervention Arm	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	432	454		
Units: responder analysis				
number (not applicable)	425	442		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events were collected through the first 5 days of trial participation.
Serious adverse events (SAEs) were collectedfor the full 90-day trial period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Intervention Arm

Reporting group description:

In the intervention group TNK-tPA is given as a single, intravenous bolus (0.25mg/Kg) immediately upon randomization. Maximum dose 50mg.

Reporting group title	Control Arm

Reporting group description:

Patients will be treated with standardof care based antiplatelet treatment – choice at the discretion of the investigator.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Frequency threshold was not applicable. Simple AEs not reported. Study only reported serious AEs.

Serious adverse events	Intervention Arm	Control Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	100 / 432 (23.15%)	80 / 442 (18.10%)	
number of deaths (all causes)	20	5	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Stroke progression			
subjects affected / exposed[2]	35 / 35 (100.00%)	33 / 33 (100.00%)	
occurrences causally related to treatment / all	35 / 35	33 / 33	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke recurrence			
subjects affected / exposed[3]	16 / 16 (100.00%)	15 / 15 (100.00%)	
occurrences causally related to treatment / all	16 / 16	15 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Symptomatic intracranial haemorrhage			

subjects affected / exposed[4]	8 / 8 (100.00%)	2 / 2 (100.00%)	
occurrences causally related to treatment / all	8 / 8	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death after symptomatic intracranial haemorrhage within 90 days			
subjects affected / exposed[5]	6 / 6 (100.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	6 / 6	1 / 1	
deaths causally related to treatment / all	6 / 6	1 / 1	
Any haemorrhage on follow-up imaging			
subjects affected / exposed[6]	62 / 62 (100.00%)	40 / 40 (100.00%)	
occurrences causally related to treatment / all	62 / 62	40 / 40	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rescue endovascular thrombectomy for index stroke			
subjects affected / exposed[7]	15 / 15 (100.00%)	10 / 10 (100.00%)	
occurrences causally related to treatment / all	15 / 15	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death within 5 days			
subjects affected / exposed[8]	8 / 8 (100.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	8 / 8	1 / 1	
deaths causally related to treatment / all	8 / 8	1 / 1	
Death at 90 days			
subjects affected / exposed[9]	20 / 20 (100.00%)	5 / 5 (100.00%)	
occurrences causally related to treatment / all	20 / 20	5 / 5	
deaths causally related to treatment / all	20 / 20	5 / 5	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed[10]	4 / 4 (100.00%)	3 / 3 (100.00%)	
occurrences causally related to treatment / all	4 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congestive heart failure			
subjects affected / exposed[11]	5 / 5 (100.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	5 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Seizure			
subjects affected / exposed[12]	3 / 3 (100.00%)	3 / 3 (100.00%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Aspiration pneumonia			
subjects affected / exposed[13]	6 / 6 (100.00%)	2 / 2 (100.00%)	
occurrences causally related to treatment / all	6 / 6	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed[14]	2 / 2 (100.00%)	4 / 4 (100.00%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Numbers are equal

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Numbers are equal

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Numbers are equal

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Numbers are equal

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Numbers are equal

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Numbers are equal

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Numbers are equal

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Numbers are equal

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Numbers are equal

[11] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Numbers are equal

[12] - The number of subjects exposed to this adverse event is less than the total number of subjects

exposed to this adverse event. These numbers are expected to be equal.

Justification: Numbers are equal

[13] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Numbers are equal

[14] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Number are equal

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Intervention Arm	Control Arm	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 432 (0.00%)	0 / 442 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2018	1. Further clarification was added on enrollment of participants who have had recent treatment with a low molecular weight heparin or direct oral anticoagulants (normal and impaired renal function) 2. Amended protocol indicated that where standard hospital supplies of tenecteplase are used there is no requirement for sites to perform temperature monitoring. Non-substantial changes are as follows: 1. Novel anticoagulants are now termed 'direct oral anticoagulants'. 2. Clarification that off-the shelf tenecteplase will be used in the study and that training will be provided on the preparation and administration of tenecteplase.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/38768626