Title Page

TEMPO-2 – A randomized controlled trial of TNK-tPA versus standard of care for minor ischemic stroke with proven occlusion

Long title: Multicentre, prospective randomized 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

Protocol Version 3.3 24th March 2017

Table of Contents

Protocol synopsis

	TEMPO-2 trial
Objectives	The primary objective: to demonstrate the efficacy of using TNK-tPA to treat minor ischemic stroke with proven arterial occlusion.
Experimental Design	A Phase 3, prospective, randomized controlled, open-label with blinded outcome assessment (PROBE) controlled trial.
Population	Up to 1274 male and female adult patients Inclusion Criteria 1. Acute ischemic stroke in an adult patient (18 years of age or older) 2. Onset (last-seen-well) time to treatment time ≤ 12 hours. 3. TIA or minor stroke defined as a baseline NIHSS ≤ 5 at the time of randomization. Patients do not have to have persistent demonstrable neurological deficit on physical neurological examination. 4. Any acute intracranial occlusion or near occlusion (TICI 0 or 1) (MCA, ACA, PCA, VB territories) defined by non-invasive acute imaging (CT angiography or MR angiography) that is neurologically relevant to the presenting symptoms and signs. An acute occlusion is defined as TICI 0 or TICI 1 flow.[1] Practically this can include a small amount of forward flow in the presence of a near occlusion AND; Delayed washout of contrast with pial vessels on multiphase CTA in a region of brain concordant with clinical symptoms and signs OR, Any area of focal perfusion abnormality identified using CT or MR perfusion – e.g. transit delay (TTP, MTT or TMax), in a region of brain concordant with clinical symptoms and signs. 5. Pre-stroke independent functional status – mRS ≤ 2. 6. Informed consent. 7. Patients can be treated within 90 minutes of the first slice of CT (or MRI) Exclusion Criteria 1. Hyperdensity on NCCT consistent with intracranial hemorrhage. 2. Large acute stroke ASPECTS < 7 visible on baseline CT scan. 3. Core of established infarction. No large area (estimated >10 cc) of grey matter hypodensity at a similar density to white matter or in the judgment of the enrolling

	neurologist is consistent with a subacute ischemic stroke. 4. Patient has a severe or fatal or disabling illness that will prevent improvement or follow-up or such that the treatment would not likely benefit the patient. 5. Pregnancy. 6. Planned thrombolysis with intravenous tPA or endovascular acute treatment. 7. In-hospital stroke unless these patients are at their baseline prior to the stroke. 8. Commonly accepted exclusions for medical thrombolytic treatment that potentially put the patient at an increased risk of bleeding. Country specific product monographs and stroke thrombolysis guidelines should be consulted. These are commonly relative contraindications (i.e. the final decision is at the discretion of the treating physician) but for the purposes of TEMPO-2 include the following: a. Significant bleeding disorder either at present or within the past 6 months b. International normalized ratio > 1.7 or known full anticoagulation with use of any standard or direct oral anticoagulant therapy with full anticoagulant dosing. [DVT prophylaxis dosing shall not prohibit enrolment]. For low molecular weight heparins (LMWH) more than 48 hours off drug will be considered sufficient to allow trial enrollment. For direct oral anticoagulants; in patients with normal renal function more than 48 hours off drug will be considered sufficient to allow trial enrollment. Patients on direct oral anticoagulants who have any degree of renal impairment should not be enrolled in the trial unless they have not taken a dose of the drug in the last 5 days. c. Dual antiplatelet therapy does not prohibit enrolment. [For patients who are known not to be taking anticoagulant therapy it is not necessary to wait for coagulation lab results (e.g. PT, PTT) prior to treatment] d. Prolonged cardiopulmonary resuscitation (> 2 minutes) within the past 2 weeks e. Acute pericarditis and/or subacute bacterial endocarditis f. Acute pancreatitis g. Severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis

	h. Neoplasm with increased bleeding risk i. Arterial aneurysm and known arterial/venous malformation j. Patients who have been acutely treated with GP2b3a inhibitors. k. Arterial puncture at a non-compressible site in the previous seven days l. Clinical stroke or serious head or spinal trauma in the preceding three months that would normally preclude use of a thrombolytic agent. m. History of intracranial hemorrhage, subarachnoid hemorrhage or other brain hemorrhage that would normally preclude use of a thrombolytic agent. n. Major surgery within the last 3 months that the treating physician considers a contraindication to thrombolytic therapy. o. Severe hypo- (< 50 mg/dL or 2.8mmol/l)or hyperglycemia (>400 or 22.2mmol/l) p. Hypertension refractory to anti-hypertensive medication such that target blood pressure <185/110 cannot be achieved before treatment. q. Known platelet count below 100,000 per cubic millimeter. [Treatment should not be delayed to wait for platelet count unless thrombocytopenia is known or suspected] *r.* Gastrointestinal or genitourinary bleeding within the past 3 months that would normally preclude use of a thrombolytic agent.
Regions	North America, Europe, Asia, Australasia
Treatments	Patients will be randomized to TNK-tPA or standard of care. In the intervention group TNK-tPA is given as a single, intravenous bolus (0.25mg/Kg) immediately upon randomization. Maximum dose 50mg. The control group will receive antiplatelet agent(s) as decided by the treating physician. Antiplatelet agent(s) choice will be at the treating physician's discretion.
Duration of Treatment	One treatment delivered acutely with a 90-day follow-up period.
Evaluation Criteria	**Primary outcome:** Return to baseline neurological functioning as measured on the mRS. Analysis will be a responder analysis where return to baseline level of neurological functioning is 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. **Secondary outcomes:** Safety, recanalization, ordinal shift analysis of mRS, NIHSS 0 at day 5 (or discharge), Euroqol, everyday activities sub-question on Euroqol, Lawton Instrumental Activities of Daily Living Scale (IADL), all cause mortality, recurrent stroke or progression, mRS 0-1 at 90days, mRS 0-2 at 90 days, mean mRS using linear regression, composite of recanalization or mRS 0-1 at 90days and mortality.
Sample Size	We test the hypothesis that there is a 9% absolute risk benefit of TNK-tPA over standard of care in the treatment of minor stroke (NIHSS 0-5) with 90% power. The rate of good outcome in the standard of care group is assumed to be 60% and 69% in the TNK-tPA group and the predicted sample size is 1228. Sample size is inflated 4% to 1274 to account for loss to follow up.
Randomization	Randomization will be 1:1 to TNK-tPA or control. Randomization will be central, computer generated and utilize a minimization algorithm to ensure balance on key variables throughout the course of the trial.
Consent	Written informed consent is required.

Trial Organization

The trial will be coordinated and executed by a steering committee based in Calgary and involve approximately 80 sites in North America, Europe, Asia and Australasia. An independent DSMB will provide safety evaluation during the trial.

The trial will be lead by principal investigator: Shelagh B. Coutts.

Co-investigators – Michael D. Hill,
Mayank Goyal
Andrew M. Demchuk
Bijoy K. Menon

The trial will be lead in Europe by Peter Kelly, at the University College in Dublin, Ireland.

Study Objectives

To demonstrate the efficacy of using TNK-tPA (tenecteplase), a thrombolytic agent that is relatively novel to the treatment ischemic stroke but well-established in the treatment of myocardial infarction, to treat minor ischemic stroke patients with proven acute symptomatic occlusions or perfusion abnormalities.

Background

Bullet Point Rationale

(i) At least 50% of ischemic stroke is initially minor.
(ii) Minor or non-disabling ischemic stroke is frequently treated conservatively with antiplatelet agents only.
(iii) Up to a third of patients with TIA or minor stroke are dead or disabled at 90 days, implying that the initial severity of presenting symptoms can be misleading.
(iv) Arterial occlusion can be demonstrated non-invasively using CT angiography or MR angiography in 10-15% of patients with TIA or minor stroke.
(v) Arterial occlusion is strongly associated with a poor outcome (dead or disabled at 3 months).
(vi) Treatment to relieve arterial occlusion is expected to result in a greater proportion of patients achieving an excellent neurological outcome.
(vii) Advantages of TNK-tPA (tenecteplase) over tPA (alteplase)
   a. TNK-tPA has greater fibrin specificity and possibly a lower intracranial hemorrhage risk compared to tPA.
   b. Lower dose TNK-tPA may offer lower risk and higher recanalization rates due to a longer serum half-life.
   c. TNK-tPA is infused using a simple bolus injection, which reduces nursing needs compared to the 60-minute tPA infusion. This would, for example, facilitate further imaging.
(viii) Proof of efficacy and safety of thrombolytic therapy in the setting of minor stroke with proven occlusion would change clinical practice.

At least 50% of ischemic stroke is minor and initially non-disabling.[2] In the "get with the guidelines" registry in the United States 41% were not treated with thrombolysis due to mild or improving symptoms.[3] These patients present with a transient ischemic attack (TIA) or minor stroke. The treatment of minor stroke with thrombolysis has always been controversial with much variation in practice. Most physicians do not treat all patients with minor deficits presenting within the standard thrombolytic window due to concerns regarding balancing the risk of hemorrhage compared to any potential reduction in disability. However a number of studies have reported that this judgment of risk may be wrong. Several groups have reported that among patients considered too mild for thrombolysis, that up to a third are dead or disabled at the time of follow up.[4-7] Recent data, involving a small subset of patients in an individual patient data meta-analysis of randomised trials of tPA suggests that thrombolysis with IV tPA among patients with minor deficits may improve outcome (OR 1.48, adjusted for age and time from onset (95%CI:1.07 – 2.06).[8]

Association of vessel occlusion and outcome in minor stroke

Minor stroke patients with documented vessel occlusion are at the highest risk of early neurological deterioration and poor outcome when thrombolysis is withheld.[6,7,9,10] These studies all used MRI to assess arterial status, which has limited the number of patients assessed in these studies.

Multi-slice helical CT scanners with CT Angiography (CTA) capability are widely available in many emergency departments. CTA uses the administration of intravenous contrast media to assess the intracranial and extracranial vasculature with high spatial resolution. The addition of CTA adds less than 5 minutes to a standard CT brain and can be safely completed in most patients.[11] CTA is one potential way of increasing the number of patients that can have early vascular imaging among patients with minor stroke. Although we expect that most sites will use CTA to meet the inclusion criteria for this study, we will allow MRI/MRA in centres that have processes in place to manage patients in this way.

We recently completed a prospective cohort study of 510 TIA and minor stroke patients (NIHSS<4) who were not treated with thrombolysis – the CATCH study.[12] All of these patients had a CT and CTA completed with a median time to CTA of 5.5 hours (IQR: 6.4 hours) showing the feasibility of using CTA to screen these patients for large artery occlusion. 10% (52/510) of patients had an intracranial occlusion. 19% (10/52) of patients with intracranial occlusion had early neurological deterioration versus 2% (9/447) in patients without occlusion, p<0.0001. We found that stroke progression occurred in both proximal and distal occlusions with similar frequency.[13] Clinical outcomes were also worse with patients having an intracranial occlusion having more disability at the time of 90 day follow up (31% versus 13%, p=0.0016) than patients without an intracranial occlusion. This was true whether the patients clinically deteriorated or not.[14] Another group has found that large artery occlusion predicts disability even among patients who have completely symptomatically resolved at baseline (i.e. TIA patients).[15] In the setting of intracranial occlusion the proposed mechanism of neurological worsening is failure of collateral blood supply. [16,17]

In summary, minor stroke patients with a documented intracranial occlusion have a higher risk of neurological deterioration and disability than those without intracranial occlusion.

Thrombolysis in minor stroke patients: efficacy and safety

The biggest reason for physicians to withhold thrombolysis is a lack of evidence to counter their concerns regarding the potential risks of treatment. Most of the thrombolysis trials completed to date have included few or no minor stroke patients. The trial with the largest number of minor stroke patients treated to date is the third International Stroke Trial (IST-3).[18] In IST-3 minor stroke was defined as a baseline NIHSS of 0-5 inclusive. IST-3 included 612 patients with an NIHSS of 0-5 (304 with tPA, 308 to control). There was no evidence of a treatment benefit with good outcome (mRS 0-1) seen in 54% (164/304) of tPA treated patients vs. 48%

(147/308) of controls (RR 1.13, 95%CI: 0.97-1.32, p=0.12).[19] A recent analysis of the Virtual International Stroke Trial Archive (VISTA) database failed to demonstrate a benefit of thrombolysis in a NIHSS 1-4 population.[20]

Symptomatic intracranial hemorrhage (SICH) was seen in 3% of tPA patients (9/304, 95%CI: 1.3-5.5) in IST-3, but not in any control patients. There was no evidence of an interaction with time for SICH (less than 4.5 hours or greater than 4.5 hours). In a subgroup analysis of the CASES study there were 77 tPA treated patients with a NIHSS score < 6 and these patients had a 2.6% (95%CI: 0.8-9%) rate of symptomatic hemorrhage.[21] In the NINDS tPA study there was a similar hemorrhage rate of 2.3% (95% CI: 0.6-12%) among patients with NIHSS score < 6.[22]

We believe that the subgroup of patients with an intracranial occlusion are the population where the risk benefit swings towards benefit. The few patients with minor stroke (NIHSS<6) that have been included in thrombolysis studies have lower rates of intracranial hemorrhage (ICH) than in more severe strokes, however the confidence intervals are wide given how few patients have been enrolled in this group [NINDS tPA[22] 2.3% (95% CI: 0.6-12%), CASES[21] 2.6% (95%CI: 0.8-9%), IST-3[19] 3% (95%CI: 1.3-5.5)]. Overall rates of symptomatic ICH have also been falling as experience with stroke thrombolysis has grown worldwide.[23]

In general, symptomatic ICH among disabling stroke patients treated with intravenous tPA has been shown to be associated with the severity of infarction, the volume of infarction shown on imaging, leukoaraiosis, the time from stroke onset, anticoagulation use and elevated serum glucose.[24] However, these variables account for only a small proportion of the variance so that to a large extent, symptomatic ICH seems a random occurrence clinically. Thus, it is our expectation that the rates of symptomatic hemorrhage will be no more than 2% among patients treated in this study. We note that patient with established infarction observable on brain imaging are at greater risk of hemorrhage. We propose to exclude patients with evidence of large volumes of infarction or clearly subacute ischemia.

Most minor stroke patients are judged to have such a good prognosis that the risk of symptomatic ICH is not worth taking. However, the rate of poor outcome is much higher than previously assumed, particularly in patients with intracranial occlusion. And, with evolving knowledge and experience with stroke thrombolysis, the safety profile has improved substantially.

Tenecteplase (TNK-tPA, TNKase™)

Tenecteplase, a genetically engineered mutant tissue plasminogen activator, has a longer half-life, is more fibrin specific, produces less systemic depletion of circulating fibrinogen, and is more resistant to plasminogen activator inhibitor[25] than alteplase.[26] These pharmacodynamic differences result in more rapid reperfusion. Tenecteplase is now the first-line intravenous thrombolytic drug for

myocardial infarction[27,28] and has shown to cause complete reperfusion with reduced ICH in comparison to alteplase in animal stroke models.[29,30]

A dose escalation safety study of tenecteplase in patients with acute ischemic stroke observed no symptomatic intracranial hemorrhages (ICHs) among 88 patients treated with doses ranging from 0.1 mg/kg to 0.4 mg/kg.[31] At 0.5 mg/kg, the study was closed early in the dose tier due to an excess of symptomatic hemorrhage. 0.5 mg/kg, is the currently approved coronary thrombolysis dose. Asymptomatic hemorrhage began to appear at 0.1 mg/kg (8% of 25 patients) and was higher at 0.2 mg/kg (32% of 25 patients) and 0.4 mg/kg (28% of 25 patients), indicating that there may be some relationship with dose. This trial was stopped prematurely due to slow enrollment.

A more recent Phase IIb study comparing thrombolysis with tPA and low dose TNK (0.1mg/Kg or 0.25mg/Kg) in moderate to severe stroke was suggestive that TNK had higher recanalization rates than tPA.[32] The study was not powered to look at clinical differences between the groups, however there were clear differences in recanalization rates at 24 hours. Complete recanalization at 24 hours was seen in 36% of the tPA group, 35% of the 0.1mg/Kg TNK group and 80% of the 0.25/kg group (p=0.002). Partial or complete recanalization was seen in 68% of the tPA group, 78% of the 0.1mg/Kg TNK and 95% of 0.25mg/Kg TNK group (p=0.02). Not only was recanalization greater with TNK, the rate of symptomatic intracranial hemorrhage was lower in both the TNK treated groups (12% versus 4% and 4%). The investigators are currently running a phase 3 trial comparing tPA with 0.25mg/Kg TNK based on these results. [33]

We recently completed a dose-escalation safety study of TNK-tPA in the treatment of minor stroke with proven occlusion – TEMPO-1 study.[34] We prospectively enrolled 50 patients with minor stroke and proven intracranial occlusion, and treated them with TNK-tPA in a 12-hour window. The first tier of 25 patients was treated at a dose of 0.1 mg/kg. The second tier of 25 patients was treated at 0.25 mg/kg. The overall rate of sICH was 2% (1/50) CI_{95} 0.5%-10.6%. There were no drug related serious adverse events in tier 1. In tier 2 there was 1 symptomatic ICH (4%, 95%CI: 0.01-20.0). Stroke progression occurred in 6% of cases. Overall, 66% had excellent functional outcome (mRS 0-1) at 90-days. Recanalization rates were high; 0.1mg/Kg (39% complete, 17% partial), 0.25mg/Kg (52% complete, 9% partial). Complete recanalization was significantly related to excellent functional outcome (mRS 0-1) at 90-days (RR 1.65: CI_{95} 1.09-2.5, p=0.026, See Figure 1).

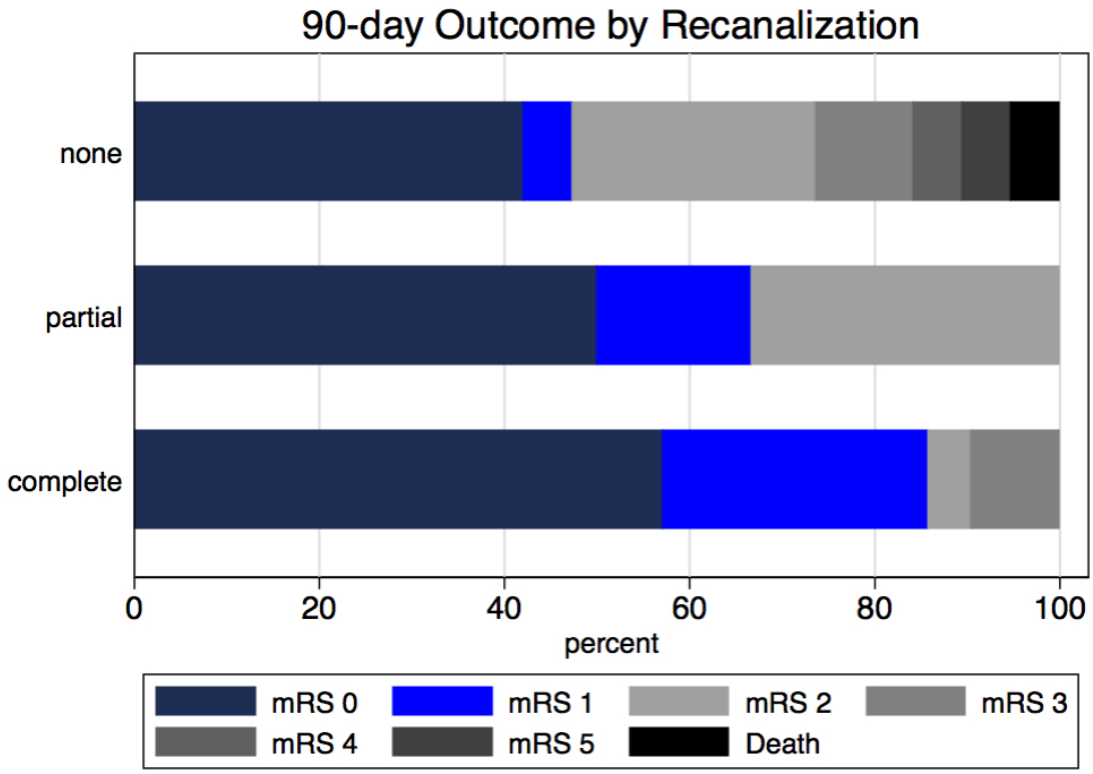

Figure 1: Figure shows the breakdown of functional outcomes at 90 days by recanalization status (complete, partial or no recanalization).

Based on the known pharmacological differences, the higher recanalization rate and an empiric dose-escalation safety study (TEMPO-1) we have chosen TNK at a dose of 0.25mg/kg.

Timing of treatment

IV tPA is in routine use in Canada up to 4.5 hours from symptom onset for treatment of disabling stroke. Patients with intracranial occlusion, but only mild symptoms are different than patients with more severe symptoms, likely due to collateral circulation.[17] These patients also have a tendency to present later than patients with more major symptoms. In the CATCH study[12] most patients deteriorated at a median time of 1 day (deterioration was mostly overnight the first night) suggesting that there may be an extended window in these patients. Many tertiary stroke centres, including the Calgary Stroke Program have been using the "small core, large area of brain at risk" paradigm to thrombolyse stroke patients outside of guideline-based care for a number of years. Different techniques have been used to identify this patient paradigm including MRI, CT perfusion (CTP) and CT Angiography (CTA). We have chosen a relatively simple approach, which is intracranial large artery occlusion (or a focal area of decreased perfusion and small area of infarcted brain). In TEMPO-1 we safely used 12 hours as our maximum potential treatment window. We showed that this was safe treatment paradigm. The reality is that most patients

present earlier rather than later. There is the occasional patient who wakes up with their deficits and their last time seen normal is close to 12 hours.

Study Design

The study will be a, prospective, randomized, open, blinded end-point (PROBE) study. Randomization will be 1:1 to 0.25mg/Kg TNK-tPA (experimental) or standard of care (control).

Primary Outcome

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 is 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. (see appendix 1).[35] Outcomes will be assessed by an individual blinded to the treatment assignment. The 90day mRS will be rated using the structured mRS questionnaire (see appendix 1). The 90 day mRS will be completed in person where possible and by telephone otherwise. The structured questionnaire has been showed to improve reliability in assessing the mRS both in person and by telephone.[35]

Secondary Outcomes

1) Proportion of patients with major bleeding: This will include an analysis of symptomatic intracranial hemorrhage alone and then combined with major extracranial hemorrhage. This is the main safety outcome.
   a) Symptomatic intracranial hemorrhage defined as new intracranial hemorrhage (ICH, SAH, IVH, SDH) associated with clinical evidence of neurological worsening, in which, the hemorrhage is judged to be the most important cause of the neurological worsening. Clinical worsening will be guided by the NIHSS score of a minimum of 2 or more points different from baseline.
   b) Major extracranial hemorrhage defined as life threatening, resulting in hemodynamic compromise or hypovolemic shock, requiring inotropic support or other means to maintain cardiac output, requiring blood transfusion of more than 2 units of packed red blood cells, or associated with a fall in hemoglobin greater than or equal to 5 g/L.
2) Proportion of patients with complete and partial recanalization (TICI 2b-3) post treatment. This will be assessed on CTA 4-8 hours post treatment. Recanalization will be assessed by the central core-imaging lab blinded to all clinical information.
3) Categorical shift analysis on the full range of the mRS (0-6).

4) Absence of disability defined as mRS 0-1.
5) Functional independence defined as mRS 0-2.
6) Comparison of the mean mRS using linear regression using the mRS as a continuous variable.
7) Lawton Instrumental Activities of Daily Living Scale (IADL)[36,37]
8) Proportion of patients with an NIHSS 0 at day 5 (or discharge from hospital if discharged before day 5)
9) Quality of life measured on EuroQol[38]
10) Quality of life as measured by the "problems with usual activities" question on the EuroQol.
11) Stroke progression and recurrent stroke.
12) All-cause mortality

Selection and Enrolment of Subjects

Inclusion criteria

1. Acute ischemic stroke in an adult patient (18 years of age or older)
2. Onset (last-seen-well) time to treatment time ≤ 12 hours.
3. TIA or minor stroke defined as a baseline NIHSS ≤ 5 at the time of randomization. Patients do not have to have persistent demonstrable neurological deficit on physical neurological examination.
4. Any acute intracranial occlusion or near occlusion (TICI 0 or 1) (MCA, ACA, PCA, VB territories) defined by non-invasive acute imaging (CT angiography or MR angiography) that is neurologically relevant to the presenting symptoms and signs. Multiphase CTA or CT perfusion are required for this study. An acute occlusion is defined as TICI 0 or TICI 1 flow.[1] Practically this can include a small amount of forward flow in the presence of a near occlusion
   AND,
   Delayed washout of contrast with pial vessels on multiphase CTA in a region of brain concordant with clinical symptoms and signs OR,
   Any area of focal perfusion abnormality identified using CT or MR perfusion – e.g. transit delay (TTP, MTT or T Max), in a region of brain concordant with clinical symptoms and signs.
5. Pre-stroke independent functional status – structured mRS ≤2.
6. Informed consent from the patient or surrogate. Surrogate consent is only allowed in countries/jurisdictions where this is approved.
7. Patients can be treated within 90 minutes of the first slice of CT or MRI. Scans can be repeated to meet this requirement; if there is no change neurologically then only a CT head need be repeated for assessment of extent and depth of ischemia.

Exclusion criteria

1. Hyperdensity on NCCT consistent with intracranial hemorrhage.
2. Large acute stroke ASPECTS < 7 visible on baseline CT scan.

3. Core of established infarction. No large area (estimated > 10 cc) of grey matter hypodensity at a similar density to white matter or in the judgment of the enrolling neurologist is consistent with a subacute ischemic stroke > 12 hours of age.
4. Patient has a severe or fatal or disabling illness that will prevent improvement or follow-up or such that the treatment would not likely benefit the patient.
5. Pregnancy. All women with the potential of being pregnant i.e. have not gone through menopause or have not undergone surgical sterilization, should have a pregnancy test prior to enrollment.
6. Planned thrombolysis with IV tPA or endovascular thrombolysis/thrombectomy treatment.
7. In-hospital stroke unless these patients are at their baseline prior to their stroke. E.g. a patient who had a stroke during a diagnostic coronary angiogram.
8. Commonly accepted exclusions for medical thrombolytic treatment that potentially put the patient at an increased risk of bleeding. Country specific product monographs and stroke thrombolysis guidelines should be consulted. These are commonly relative contraindications (i.e. the final decision is at the discretion of the treating physician) but for the purposes of TEMPO-2 include the following:
    a. Significant bleeding disorder either at present or within the past 6 months
    b. International normalized ratio > 1.7 or known full anticoagulation with use of any standard or direct oral anticoagulant therapy with full anticoagulant dosing. [DVT prophylaxis dosing shall not prohibit enrolment]. For low molecular weight heparins (LMWH) more than 48 hours off drug will be considered sufficient to allow trial enrollment. For direct oral anticoagulants; in patients with normal renal function more than 48 hours off drug will be considered sufficient to allow trial enrollment. Patients on direct oral anticoagulants who have any degree of renal impairment should not be enrolled in the trial unless they have not taken a dose of the drug in the last 5 days. Dual antiplatelet therapy does not prohibit enrolment. [For patients who are known not to be taking anticoagulant therapy it is not necessary to wait for coagulation lab results (e.g. PT, PTT) prior to treatment]
    c. Prolonged cardiopulmonary resuscitation (> 2 minutes) within the past 2 weeks
    d. Acute pericarditis and/or subacute bacterial endocarditis
    e. Acute pancreatitis
    f. Severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
    g. Neoplasm with increased bleeding risk
    h. Arterial aneurysm and known arterial/venous malformation
    i. Patients who have been acutely treated with GP2b3a inhibitors.
    j. Arterial puncture at a non-compressible site in the previous seven days

k. Clinical stroke or serious head or spinal trauma in the preceding three months that would normally preclude use of a thrombolytic agent.
l. History of intracranial hemorrhage, subarachnoid hemorrhage or other brain hemorrhage that would normally preclude use of a thrombolytic agent.
m. Major surgery within the last 3 months that the treating physician considers a contraindication to thrombolytic therapy.
n. Severe hypo- (< 50 mg/dL or 2.8mmol/l) or hyperglycemia (>400 or 22.2mmol/l)
o. Hypertension refractory to anti-hypertensive medication such that target blood pressure <185/110 cannot be achieved before treatment.
p. Known platelet count below 100,000 per cubic millimeter. [Treatment should not be delayed to wait for platelet count unless thrombocytopenia is known or suspected]
q. Gastrointestinal or genitourinary bleeding within the past 3 months that would normally preclude use of a thrombolytic agent.

Selecting Patients

The principles of patient selection are based upon the broad criteria of:

a. TIA or 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 consistent with the presenting symptoms or consistent with the suspected pathophysiology of the presenting symptoms that suggests well-evolved infarction, judged to be potentially prone to bleeding.

The most challenging of these principles is (c) since it requires judgment and imaging interpretation. We know from imaging studies using MR perfusion imaging that regions of very low CBV are prone to hemorrhage.[39] Yet, using MR diffusion imaging it can be shown that many patients with minor lesions who then present with subsequent major stroke and are treated with IV tPA do not suffer hemorrhage.[40] Clinically, it has been a maxim of stroke thrombolysis that among patients who present with a TIA-like presentation who neurologically resolve and then subsequently deteriorate, the clock can be reset to the time of deterioration. Yet, we know that 50% or more of patients with TIA/minor stroke presentations have MR defined small ischemic lesions.[41,42] Empirical clinical experience suggests that thrombolysis in presence of small lesion volumes is safe.

Patient who are at increased risk of hemorrhagic complications should not be enrolled in the trial. Generally, standard thrombolytic agent contraindications will be considered at the discretion of the treating physician as exclusion criteria. The use of tenecteplase or other thrombolytic agents in patients who are taking or have been recently taking direct oral anticoagulant medicine is uncertain. This is

particularly true for the medicines that are dependent upon normal renal function for excretion. There are 4 currently marketed direct oral anticoagulants: Dabigatran, rivaroxaban, apixaban, betrixaban. Therefore, patients with any degree of renal failure who have taken one or more doses of these medicines in the prior 5 days are excluded. Patients with normal renal function are excluded if they have taken one or more doses of these medicines in the prior 48 hours.

Enrolment

Patients will be screened using the usual stroke team process of care at the site. Candidates for enrolment will be approached for consent. Since all subjects are expected to be relatively mildly affected clinically at presentation, many/most will be able to provide consent themselves. In certain countries/jurisdictions an incompetent patient, who otherwise meets criteria, may still be enrolled with the consent of a surrogate or legally authorized representative. All patients or their surrogate must provide written informed consent.

All patients will be evaluated clinically and then undergo brain imaging using CT followed immediately by a CT angiogram. If they remain eligible, after review of clinical testing, imaging and laboratory testing, they will be immediately enrolled and treated. All patients will be treated within 90 minutes of the first slice of the baseline CT. In sites where MRI/MRA is routinely used this can be substituted for CT/CTA. In all parts of the protocol MRI/MRA can be substituted for CT/CTA.

A patient is considered enrolled into the trial at the point (date and time) of randomization. If randomized to active treatment they should immediately receive study drug. Randomization is considered time 0. A patient who provides consent but is not enrolled into the trial is considered a screen failure.

Study Interventions

Randomization will be 1:1 to TNK-tPA (experimental) or standard of care antiplatelet agents (control).

Experimental: 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 standard manufacturers' instructions for use. Please refer to current Product Monograph for details on reconstitution and infusion of the drug.

Control: Patients will be treated with standard of care based antiplatelet treatment – choice at the discretion of the investigator. Low dose aspirin (single agent) will be the choice of most physicians, however given the results of the FASTER trial[43] and the recently published CHANCE trial[44] some will chose to use the combination of aspirin and clopidogrel. As this is a multi-centre, international trial where local practices will vary, rather than mandating a specific antiplatelet agent, we will allow the local investigator to chose which antithrombotic regime should be used.

Standard of care medication(s) should be given immediately upon randomization.

Patients will undergo a study CT angiogram of the intracranial circulation between 4-8 hours after treatment to determine the biological effect of the drug - whether the occluded artery has recanalized or not. Any patient who has neurological worsening should have standard of care brain imaging completed to rule out intracranial hemorrhage.

All patients will have standard of care medical management on an acute stroke unit and undergo follow-up imaging at 24 hours with CT or MR. Use of MR will be encouraged.

Randomization: Concealment and Blinding

Randomization will be completed by a computer generated minimization algorithm – minimal sufficient balance randomization. This will ensure balance throughout the trial, based on key variables. This algorithm will be developed centrally and the details will not be available to the treating sites. The minimization algorithm preserves balance on pre-specified prognostic variables. Variables that will be included in the minimization algorithm are age, sex, baseline NIHSS score, pre-morbid mRS, and time of randomization (under 4.5 hours versus not). These are the key variables known to influence outcome in minor stroke.[10,14,45] Randomization will be dynamic and generated in the moment via a web-based system; thus a randomization list does not exist. The result will be random allocation that is fully concealed. Randomization will be biased coin that will vary from fully balanced (50:50) to biased (65:35) dependent on what characteristics been previously enrolled have. The system will be enabled for smart-phone, tablet, laptop or desktop computer use.

Study Drug

The trade name for tenecteplase is TNKase™ in North America and Metalyse™ in Europe and Australasia. Off the shelf tenecteplase will be used in this study. Staff will be trained in the mixing and administration of the drug.

STORAGE AND STABILITY

Store lyophilized TNKase™ (or Metalyse™) tenecteplase, TNK-tPA) at controlled room temperature (2-30°C) not to exceed 30°C or under refrigeration (2°C - 8°C). If standard hospital supplies are being used then temperature monitoring is not required. Do not use beyond the expiration date stamped on the vial. Unused reconstituted TNKase™ (in the vial) may be stored at 2°C - 8°C and used within 8 hours. After that time, any unused portion of the reconstituted material should be discarded.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms:

There are different sized vials of TNKase™ (or Metalyse™) available in different countries. In Canada for example 50mg vials are available.
Each 50mg vial of TNKase™ (or Metalyse™) is packaged with one 10ml vial of Sterile Water for Injection for reconstitution. For other vial sizes follow the reconstitution instructions included with the drug. Reconstitution of 50mg of tenecteplase in 10 ml of sterile water results in a solution concentration of 5mg/ml. For other sizes of tenecteplase follow the reconstitution instructions included with the drug. The dose is 0.25 mg/kg or 0.05ml/kg.

Composition:

TNKase™ is a sterile, white to off-white, lyophilized powder for single intravenous (IV) bolus administration after reconstitution with Sterile Water for Injection, USP.

50 mg (10,000 units) / vial

Tenecteplase* 52.5 mg
L-Arginine 0.55 g
Phosphoric Acid 0.17 g
Polysorbate 20 4.3 mg
*This includes a 5% overfill so that each vial will deliver 50 mg of tenecteplase.

Packaging:

Each 50 mg vial of TNKase™ is packaged with one 10 mL vial of Sterile Water for Injection, USP
for reconstitution and one B-D
® 10 cc Syringe with TwinPak® Dual Cannula Device.

Schedule of Assessments

	Baseline	4-8 h	Day 1 (24 ±8 h from randomization)	Day 5 or discharge (±1 d)	Day 90 (±14 d)§
Informed consent	X				
Regained capacity consent (if needed)					X
History and examination	X				
Weight	X±	X±	X±	X±	
NIHSS	X		X	X	X
mRS					X
Pre-stroke mRS¶	X				
EuroQol					X
Lawton Instrumental Activities of Daily Living Scale (IADL)					X
NCCT head or MR	X*		X***		
CTA COW or MRA	X*	X**			
Full emergency stroke labs	X‡				
Creatinine	X		X		
ECG	X‡				
Adverse event assessment		X	X	X	
Serious adverse event assessment		X	X	X	X§
Prior medications	X‡				
Concomitant medications§	X	X	X	X	

* MRI/MRA can be substituted for baseline CT/CTA at the discretion of the local site.
**4-8 hours CTA Circle of Willis (COW). At the discretion of the local investigator the follow up CTA can be not completed if the eGFR is <40 ml/minute or there was an allergic reaction to the baseline scan.

***Day +1 NCCT head may be supplanted by an MR head including diffusion weighted imaging (DWI) and gradient echo (GRE) at the discretion of the local site.
¶ The pre-stroke mRS is an estimate of the pre-stroke score and is based on the history given by the patient/family.
‡ These tests are required at baseline. Blood should be drawn at baseline, but results are not required prior to randomization. In certain countries as recommended by national guidelines; blood work for group and hold (type and screen) should be collected. ECG should be done within 6 hours of hospital admission, but is not required prior to randomization. Prior medications should be collected but are not required prior to randomization.
§ Concomitant medications are collected out to Day 5 or in conjunction with any SAE. Collect concomitant medications at 90days only as part of the SAE narrative only on patients with SAEs.
All 90 evaluations should be performed by an evaluator blinded to the acute intervention. We are encouraging that this visit be completed in person, but if this is not possible a telephone follow up can be substituted.
d = days; h = hours
± Actual weight must be performed once by Day 5 or Discharge and recorded, not necessary to be done at all time points.

Laboratory Evaluations

Routine blood work will be taken in the emergency department. This will include PT/PTT, CBC, electrolytes, glucose and creatinine. The coagulation status must be known prior to treatment among patients who are known to be on any form anticoagulation therapy. ECG should be completed at baseline either prior to treatment or within 6 hours of treatment.

If the estimated GFR is subsequently found to be <40 ml/minute or there was an allergic reaction to the baseline CTA then the repeat CTA should not be completed. This is not a protocol deviation.

Clinical evaluations

All patients will have a stroke history and physical before treatment is commenced. All investigators will be trained in both the NIHSS and mRS. Patients will be assessed at 24 hours or at the time of any deterioration using the NIHSS. At 5 days (or at discharge from hospital if sooner) patients will have an NIHSS completed. At 90 days the NIHSS, Euroqol, Lawton Instrumental Activities of Daily Living Scale (IADL) and mRS will be completed by a blinded investigator. The mRS will be rated using the structured mRS questionnaire.[35] The investigator completing the 90d outcome assessment should be a blinded site trial investigator, sub-investigator or coordinator defined as absence of involvement in the first 48 hours of treatment of the patient. If not feasible to complete in person this interview can be completed by telephone.

Prohibited medications and procedures

In the experimental treatment group: no antiplatelet agent, other antithrombotic medicines should be given within the first 24 hours (+/- 8h) of the treatment. These can be started, if clinically indicated, once the 24-hour (+/- 8h) follow-up CT has been completed and shows no clinically significant intracranial hemorrhage. In practice, this means that if there is no hemorrhage on follow-up brain imaging, antithrombotic or antiplatelet medicines may be given without restriction. If there is hemorrhage, a judgment must be made about the relative safety of antiplatelet or antithrombotic medicine. For example, it is medically appropriate if the

hemorrhage is limited or small or simply petechial (hemorrhagic infarction type) and the benefit is judged to outweigh the risk.

It is expected that a majority of the control group will be treated with single (or dual) antiplatelet therapy. Given the presence of a large artery occlusion we would recommend not immediately using heparin or one of the direct oral anticoagulants even in the presence of atrial fibrillation. We would recommend that the use of anticoagulants is delayed for at least 24 hours in both groups of patients. However the final decision is left to the judgment of the treating physician.

Patients should not undergo endovascular thrombectomy or thrombolysis outside of the trial protocol. This is considered a protocol violation. However, in the event of a clinical deterioration and this type of protocol violation, the patients will be considered to have suffered an early recurrent stroke (which is a pre-specified secondary outcome), even if they are cured by endovascular therapy. Adverse events that occur related to such treatment will be recorded and adjudicated accordingly.

Guidelines for Clinical Care

It is expected that subjects will receive the best usual standard of stroke unit care. All subjects are expected to be admitted to hospital as part of routine standard of care. Most subjects will have mild symptoms and recover in 1-2 days and likely will be subsequently discharged home.

It is expected that all subjects will undergo a routine work-up for the mechanism of their stroke and be treated appropriately and definitively. This is critically important because subjects with mild stroke secondary to large artery disease are at the highest risk of early recurrent stroke. [46] We wish to prevent recurrent stroke from confounding the 90-day clinical outcome such that patients who are well at discharge remain that way for the duration of the 90-day follow-up period.

We expect that most patients with atrial fibrillation will be anti-coagulated. Patients with symptomatic carotid artery stenosis should undergo carotid revascularization early and definitely within 2 weeks of stroke onset.[47] Risk factors, including hypertension, elevated cholesterol, diabetes mellitus, tobacco smoking, should be treated appropriately and aggressively according to current standards of care.

We expect patients to receive adequate hydration to prevent renal complications of the use of radio-contrast media for diagnostic imaging. While this medication is generally extremely safe, simple hydration can prevent renal complications, particularly among patients with baseline borderline renal function and among those with diabetes mellitus. Further, patients with ischemic stroke are generally slightly hypovolemic at baseline. We recommend use of intravenous normal saline (0.9% saline) infusion at 1.5 – 2.0 cc/kg/h until the patient is eating and drinking

safely and well. Therefore, for the typical patient this will mean IV NS at 75-150 cc/h overnight only. We do not recommend the use of bicarbonate solutions or N-acetyl-cysteine solutions.

For patients that are disabled from their stroke and require a longer in-patient stay and/or rehabilitation, it is expected that they will receive standard stroke unit care to prevent complications. These include:

- DVT prophylaxis for patients who are bed-bound or primarily bed-bound
- Swallowing assessments and prevention of aspiration pneumonia
- Early mobilization and physiotherapy to prevent skin breakdown, pneumonia, DVT/PE
- Early diagnosis and treatment of fever

Imaging

All imaging completed of the brain, CT, CTA, and MRI in the first 48h will be rendered anonymous and sent to Calgary for central adjudication. Minimally the baseline, 4-8h CTA and the 24-hour imaging should be included.

Clinical Management of Adverse Experiences

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Adverse events can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality. Adverse events occur after enrolment and are defined as not being present prior to enrolment. For example, a patient with known episodic gouty arthritis of the great toe, who develops an attack of gout, is not considered to have suffered an adverse event; the event was known prior to enrolment. A patient who develops a new diagnosis of gout during the study period is judged have suffered an adverse event. This is reportable as an adverse event even though it is most likely entirely unrelated causally to the study drug, but is instead only associated with study drug use temporally. Adverse events should be managed according to the best current standard of care.

Serious adverse events (SAEs) are those adverse events that are life threatening, require a surgical or medical procedure to prevent disability or death, result in admission to hospital, prolongation of hospitalization or transfer to an ICU, or result in death. A SAE can also be an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Any new diagnosis of cancer (made after study enrollment) is considered an important medical event. A SAE is also an event that results in a congenital anomaly or birth defect, but this is an unlikely consideration for this trial since all or nearly all participants will not be of reproductive potential. Serious adverse events should be managed according to the best

current standard of care.

Adverse Event Reporting and Review

Adverse events will only be collected through the first 5 days of trial participation. Adverse events should be reported as they occur on the eCRF. There are no timelines for reporting simple adverse events. Documentation must be supported by an entry in the subject's file. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product as judged by the Investigator, action taken and outcome.

Serious adverse events (SAEs) will be collected for the full 90-day trial period. SAEs must be reported **immediately by the investigator within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the SAE**. SAEs will be reviewed by the trial medical monitor. SAEs will be reported to the appropriate regulatory authority in accordance to the relevant regulations and legislation in that region and state/country. Because the adverse event profile of TNK-tPA is well known due to the experience of its use for coronary thrombolysis, we do not predict that there will be unexpected adverse events.

Pregnancies occurring in study subjects will be treated procedurally as SAEs. Pregnancies occurring in study subjects after signing informed consent should be reported separately on Pregnancy Report Form.

Data Safety and Monitoring Board (DSMB)

Members of the DSMB will be acknowledged publically but will not be considered authors for any manuscripts that arise from this trial.

Expected Drug Reactions

For expected adverse drug reactions (ie. with relationship to Metalyse or TNKase) investigators are directed to the product monograph.

Criteria for Intervention Discontinuation

Because the study drug is a delivered by a single intravenous bolus injection, it will not be possible to discontinue the intervention.

In the event that a subject withdraws consent for follow-up in the study, that subject will be discontinued from the trial on the date of their withdrawal of consent. Data collected prior to this date will be included in the final study report.

Statistical Considerations

A sample of 1228 patients allows us to demonstrate a 9% absolute risk difference (60% → 69% primary outcome) with 90% power between intervention and control groups.

The recent pooled thrombolysis showed an effect size of 10% in the subset of minor stroke patients treated with thrombolysis.[8] Enrollment in the trials included in the meta-analysis did not require patients to have an intracranial occlusion, thus it is likely that the majority of these patients did not have an intracranial occlusion. Thus although we expect that the effect size is higher in a population that only includes patients with intracranial occlusion we will conservatively estimate an overall 9% effect size with a change in proportion with excellent neurological outcome from 60% to 69%. The sample size for each group is 614 (1228 total).

Adding 4% loss to follow up gives a sample size estimate of 1274 patients (637 in each treatment group). There will be ongoing monitoring for safety and full details will be available in a formal safety plan. A single interim analysis for futility and efficacy will be conducted at approximately two-thirds patient enrolment (n=840). Standard O'Brien Fleming boundaries will be used to establish the alpha spending function. Full details will be available in the DSMB charter.

It is possible that after central imaging review some patients will be enrolled in violation of the protocol or the treatment protocol may be breeched due to the dynamic nature of acute stroke. This may occur entirely in the best interests of patient care. In the primary analysis, all randomized patients will be included in the final analysis for safety and clinical outcome (ITT analysis). The safety population will be defined as all patients who receive any dose of study drug. The per-protocol population will be defined as all patients who received any dose of study drug and met all the inclusion and exclusion criteria.

Secondary analyses will include analysis of the pre-stated secondary outcomes and multivariable analyses of both the primary outcomes and pre-stated secondary outcomes. A formal Statistical Analysis Plan will be documented prior to breaking of the blind.

Data Collection and Management Overview

Data will be housed and managed in a custom database at the Hotchkiss Brain Institute Clinical Research Unit in Calgary, AB, Canada using regulatory compliant data systems.

Human Subjects

Local Regulations / Declaration of Helsinki

The Sponsor-Investigator (and any Participating Site Investigators) will ensure that this study is conducted in full conformance with the principles of the "Declaration of

Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline or with local law if it affords greater protection to the patient.

Ethics approval

This protocol and the informed consent document and any subsequent modifications are reviewed and approved by the local ethics committee responsible for oversight of the study. Approval from the committee must be obtained before starting the study, and should be documented in a letter to the Sponsor-Investigator (and any Participating Site Investigators) specifying the date on which the committee met and granted the approval. A signed consent form must be obtained from the subject. In certain countries/jurisdictions where permitted, for subjects who cannot provide consent themselves, a legally authorized representative, or person with power of attorney, may sign the consent form. The consent form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form must be given to the subject, the legally authorized representative, or the person with power of attorney; and this fact must be documented in the subject's record.

If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information, given a copy of the revised form, and give their consent to continue in the study.

Conditions for Terminating the Study

The Sponsor-Investigator reserves the right to terminate the study at any time. Should this be necessary, the Sponsor-Investigator will work with any Participating Site Investigators to arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Sponsor-Investigator (and any Participating Site Investigators) will assure that adequate consideration is given to the protection of the patients' interests.

Confidentiality

All imaging, evaluation forms, reports, and other records that leave the site are identified only by the site and subject number to maintain subject confidentiality. All records are kept in a locked file cabinet. Clinical information is not released without written permission of the subject, except as necessary for monitoring by ethics committees, regulatory bodies, the sponsor, or the sponsor's designee.

All study investigators at the clinical sites must ensure that the confidentiality of personal identity and all personal medical information of study participants is maintained at all times. Country specific privacy regulations where applicable, must be followed. On the CRFs and other study documents or image materials submitted to the CRU, the subjects are identified only by study identification codes.

Personal medical information may be reviewed for the purpose of verifying data recorded in the CRF by the site monitors. Other properly authorized persons, such as the regulatory authorities, may also have access to these records. Personal medical information is always treated as confidential.

Site Monitoring

All sites will have remote data monitoring conducted by the central trials staff. Data will be checked for completeness, logic, and validity. Queries will be sent to sites to verify data as required.

For on-site monitoring a variety of risk-based monitoring models will be used. This may include both trained employees and industry experienced independent contractor clinical research monitors. Details of monitoring will be in a separate site monitoring plan.

Study Documentation, CRFs and Record Keeping

Investigator's Files/Retention of Documents

The Sponsor-Investigator (and any Participating Site Investigators) must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories: (1) Investigator's Study File; and (2) patient clinical source documents.

The Investigator's Study File will contain the protocol/amendments, Case Report and Query Forms, ethics correspondence and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc. Some or all of these files may be stored electronically.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, diagnostic imaging, pathology and special assessment reports, signed ICFs, consultant letters, and patient screening and enrollment logs. The Sponsor-Investigator (and any Participating Site Investigators) must keep these two categories of documents on file for 25 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

Source Documents and Background Data

Any Participating Site Investigators shall supply the Sponsor-Investigator on request with any required background data from the study documentation or clinic records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In case of special problems and/or governmental

queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

Audits and Inspections

The Sponsor-Investigator and any Participating Site Investigators should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor-Investigator or designee or to health authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents.

Case Report Forms

For each patient enrolled, a CRF must be completed and signed by the Sponsor-Investigator (and any Participating Site Investigator) or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the CRF.

All forms should be filled out clearly and legibly. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the Sponsor-Investigator (and any Participating Site Investigators) or his/her authorized delegate. The Sponsor-Investigator (and any Participating Site Investigators) should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor-Investigator in the CRFs and in all required reports.

Publication and Presentation Policy

The trial executive committee will be co-authors on all publications and presentations. The primary author list for the primary publication will consist of the executive committee and the site principal investigator at each of the sites. The results of this study may be published or presented at scientific meetings.

Ancillary Studies Policy

Ancillary or sub-studies may be considered by the trial executive committee. Important principles that guide the addition of ancillary studies are:

(1) no patient shall be enrolled in a concurrent investigational drug/device trial during the study period.

(2) concurrent enrollment of a TEMPO-2 study patient in a site specific observational cohort study is allowable, where the following conditions are met:

a. the executive committee is notified
b. the concurrent study does not interfere with any study follow-up procedures or potentially confound the outcome of the TEMPO-2 trial

c. the site PI of the concurrent study explicitly acknowledges that the treatment given in the TEMPO-2 trial may confound the outcome of the site-specific concurrent study
d. the patient may not be included in any publication or report until the TEMPO-2 study has been concluded and published.

(3) Ancillary or sub-studies shall be vetted and approved by the trial executive committee.

Data-sharing plan

The Executive Committee will follow the spirit of the NIH policy on data-sharing [http://grants2.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm]. In addition, the Executive Committee will follow the CIHR guidelines on public access to trial results and make the results available as free-access using PubMed. Upon completion of the TEMPO-2 Trial, a public use database will be prepared by stripping any and all personal identifiers. The public use database, consisting of several data files, should contain: (1) baseline and demographic characteristics; (2) outcomes assessments; (3) CT/MRI data; (4) concomitant medications and procedures; and (5) adverse events. Each data file is made available as a formatted SAS dataset or other electronic format. The data files are distributed along with the data dictionary and a brief instruction ("Readme") file. These data files will be made available to the public only after all major manuscripts (including secondary analysis papers) of the Trial are accepted for publication in peer-reviewed journals.

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Appendix 1: Structured mRS - Taken from Bruno et al.[35]