TEMPO-1. Statistical Analysis Plan v1.2

The TEMPO-1 study is a safety in dose-escalation and feasibility trial designed to assess the safety and feasibility of enrolling patients with minor stroke and proven arterial occlusion, and then treating them with low-dose thrombolytic TNK-tPA.

The design is a prospective, observation cohort study. Two sequential cohorts will be treated with TNK-tPA at separate doses. Since all patients will be treated. The relevant outcomes are simply proportions and distributions.

Enrolment in the study is only compatible with drug treatment. Because treatment is a single bolus injection of study drug, all treated patients will be in the analysis cohort for both safety and efficacy.

There is no randomization. The study is open-label with blinded outcome adjudication. The patient is considered enrolled in the trial as soon as drug is administered.

Missing data will be minimized if at all possible. Outcomes will be retrieved on all patients with active and determined follow-up. If a subject is missing one of the outcomes, he will be excluded from the determination of the proportions. No outcome data will be imputed.

Analysis Plan - Outcomes

1. Safety.

Proportion of patients with serious adverse safety events.
-all events
-related to study drug (possibly / probably / definite)

Primary Events

(i) 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. Baseline NIHSS score is defined as the time immediately prior (within 10 minutes) to drug administration.

(ii) 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.

(iii) Life-threatening angioedema defined as severe airway obstruction requiring intubation.
(iv) Life-threatening thrombolysis associated hypotension defined as a drop in blood pressure that requires inotropic support.

Secondary and Efficacy Events

(i) Asymptomatic or minor or moderate bleeding—defined as requiring a transfusion of 2 units of packed red blood cells or less, not severe as defined above, or associated with a fall in hemoglobin of less than 5 g/L; minor—defined as bleeding not requiring transfusion, not causing hemodynamic compromise, usually including hematoma, subcutaneous bleeding, oozing from puncture sites, and may require modification of drug regimen; and asymptomatic—defined as bleeding that results in no symptoms.
(ii) Complete neurological and functional recovery at 30 days defined as: NIHSS 0 and mRS 0 and absence of all neurological symptoms and signs
(i) Complete neurological and functional recovery at 90 days defined as:
a. NIHSS 0-1 and mRS 0-1 and Barthel Index > 90 AND
b. Absence of all neurological symptoms and signs AND
c. Complete lifestyle recovery such that the patient is back to all prior activities; specifically, this includes driving a car, working and/or active leisure activities.
(ii) Proportion of patients with any recurrent stroke event (stroke or TIA) within 90 days.
(iii) Recanalization defined on follow-up 4-8 hour CTA.
(iv) Proportion of patients with observable infarction on follow-up imaging.
(v) Volume of infarction.
(vi) Recurrent stroke or progression of stroke with any persistent functional neurological worsening at 24 hours after enrolment.
(vii) Recurrent stroke or progression of stroke with any persistent functional neurological worsening with NIHSS score 4 or more points greater than at enrolment

1. Feasibility

Rate of patient enrolment in time. The denominator will be the actual number of days when the study is open to enrolment.

Reporting will be with standard descriptive statistics. All proportions will be reported with exact confidence limits.