Eliquis Acute Stroke Safety Evaluation

EASSE

Version 2.0

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Principal Investigator: Dr. Kenneth Butcher

7-132D Clinical Sciences Buidling

11350-83 Avenue

Edmonton, Alberta T6G 2B7

Phone: 780-248-1927

Email: ken.butcher@ualberta.ca

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conduct according to all stipulations of the protocol, including all statements regarding confidentiality and according to local legal and ethical requirements and applicable Canadian regulations and ICH guidelines.

Qualified Investigator/Principal Investigator

Name: _____

Signed: _____ Date: _____(dd/mmm/yyyy)

Site Name: _____

Address: _____

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PROTOCOL SUMMARY

Title: EASSE – Eliquis Acute Stroke Safety Evaluation

The Eliquis Acute Stroke Safety Evaluation (EASSE) is an investigator initiated, prospective, open label, single arm phase IV study.

Overall Study Aims:

1. Demonstrate the safety of early anticoagulation with apixaban following cardioembolic stroke and TIA.
2. Document the rate of recurrent cerebrovascular ischemic events.

Primary Outcome: The primary endpoint is the rate of symptomatic hemorrhagic transformation (PH2) associated with clinical deterioration, defined as worsening of NIHSS score of 4 or more points within 30 days of initiating anticoagulant therapy.

Secondary Outcome: The major secondary endpoint is the rate of any parenchymal haemorrhage (PH1 or PH2) seen on on follow-up MRI scans at 7±2 days post-enrolment. Other secondary endpoints include recurrent TIA/Ischemic Stroke within 90 days of enrolment, and systemic hemorrhagic complication rate within 90 days of enrolment

Population: 50 participants will be enrolled. Participants are males and females, ≥18 years of age, with TIA or ischemic stroke and a known history of or demonstrated atrial fibrillation (paroxysmal or persistent), who can be treated with apixaban following stroke.

Phase: IV

Protocol Therapy: Patients will be treated with apixaban within 14 days of symptom onset. Patients fulfilling at least two (2) of the following characteristics, will have received a reduced dose of ELIQUIS 2.5 mg twice daily: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 133 μmol/L (1.5 mg/dL). All other patients will have received 5 mg dose taken orally twice daily.

Study Duration: It is estimated that recruitment will take place over 2 years in the three participating centres. Enrolment is anticipated to commence by the beginning of 2017.

Subject Participation Duration: All patients will be assessed clinically at Day 7 and Day 90.

1.0 Background and Rationale

1.1 Timing of Anticoagulation after Cardioembolic TIA/Stroke

It is clearly established that patients with atrial fibrillation who have suffered a stroke/TIA are at high risk for recurrence and require long-term anticoagulation. What is unknown is the optimal timing of anticoagulation after an ischemic stroke has occurred. Following cardioembolic stroke, atrial fibrillation patients are at risk for early recurrent thrombo-embolism. Estimates of the rate of recurrent stroke in this setting vary widely. Previous studies have indicated new ischemic strokes occur at rates anywhere from 3% to 20% within two weeks of the index event. Data from the Ontario Stroke Registry demonstrated that half of the ischemic stroke cases occurred within the first 2 days after the initial event. This is the primary rationale for early anticoagulation after cardioembolic stroke. There is some evidence that early anticoagulation is associated with improved outcomes after ischemic stroke. Indeed, it has been shown that early heparin use does reduce recurrent ischemic stroke risk by 2.1%, but this is offset by a 1.7% increase in the rate of HT. Studies of low molecular weight and unfractionated heparin use in acute stroke have generally indicated these agents are associated with moderately increased risk of HT. There are currently no data indicating the frequency of HT associated with early warfarin treatment, without heparin bridging.

Based on the above evidence, current best practice guidelines recommend against urgent anticoagulation in patients with moderate to severe ischemic stroke, however, due to the elevated risk of hemorrhagic transformation (HT) immediately after stroke. A specific time point at which to begin anticoagulation is not recommended in guideline statements. This clinical equipoise has resulted in significant variation in practice patterns. Currently, most CSC physicians base the timing of anticoagulation on clinical severity and infarct size, as seen on CT scan. Most physicians will defer anticoagulation anywhere from 5 to 14 days after ischemic stroke when infarct volume is extensive. In patients with small infarct volumes, assessed with CT or MRI, however, anticoagulation is often begun within 24-72 hours of stroke onset, and in some cases immediately after clinical assessment and CT scan.

Currently, the Alliance has no data related to early use of apixaban after TIA or ischemic stroke. In ARISTOTLE, patients were not eligible for enrolment/randomization within 7 days of ischemic stroke or TIA. The contraindications section of the product monograph states apixaban should not be used in patients with ‘Lesions or conditions at increased risk of clinically significant bleeding, e.g., recent cerebral infarction (ischemic or hemorrhagic)’. This is therefore an area of clinical equipoise. As with warfarin (with/without heparin bridging), stroke specialists will make individual treatment decisions, based primarily on the extent of infarction visible on CT brain scan.

Although a randomized study of delayed versus early anticoagulation with apixaban will ideally answer this question, at the moment, there is no feasibility or safety data. There is also insufficient data in the present literature to indicate what the true event rates for both symptomatic hemorrhagic transformation and recurrent cerebral ischemia are. These data can be obtained by prospectively collecting clinical and imaging data from patients who are treated, as per standard clinical practice in most Canadian stroke centres, within this 7-day period of clinical

uncertainty. The results of this registry will be used to assess the safety and feasibility of a larger randomized controlled trial of early versus delayed apixaban use after stroke/TIA.

2.0 Study Objectives

2.1 Overall Aim and Hypothesis

The primary aim of the Eliquis Acute Stroke Safety Evaluation registry is to demonstrate the safety of early anticoagulation with apixaban following cardioembolic stroke and TIA. Safety will be established by demonstrating low rates of hemorrhage in this setting. The secondary study objective is to document the rate of recurrent cerebrovascular ischemic events. It is fully recognized that this uncontrolled registry study is not properly designed and underpowered to demonstrate a reduction in cerebrovascular ischemic events.

We hypothesize that early initiation of apixaban within the first 14 days of stroke or TIA is not associated with increased symptomatic intracranial haemorrhage.

2.2 Outcome Variables

2.2.1 Primary Outcome:

Symptomatic Hemorrhagic Transformation Rate (PH2) associated with clinical deterioration, defined as worsening of NIHSS score of 4 or more points within 30 days of initiating anticoagulant therapy.

2.2.2 Secondary Outcomes:

1. Any parenchymal haemorrhage (PH1 or PH2) on follow-up MRI scan at 7±2 days post-enrolment.
2. Recurrent TIA/Ischemic Stroke within 90 days of enrolment.
3. Systemic hemorrhagic complication rate within 90 days of enrolment.

3.0 Study Design

The Eliquis Acute Stroke Safety Evaluation (EASSE) is an investigator initiated, prospective, open label, single arm phase IV study.

Consecutive patients with atrial fibrillation (new onset or previous history) with acute ischemic stroke or TIA will be screened from Emergency Department or stroke unit. A total of 50 male and female patients will be recruited within 24 hours of initiation of apixaban after TIA or stroke. Informed consent will be obtained from the patient or substitute decision maker, in all cases prior to enrolment. Patients will be approached by the Stroke team or stroke unit attending physicians participating in the trial.

4.0 Enrolment Criteria

4.1 Inclusion Criteria

1. Male or female patients
2. Must be ≥ 18 years of age.
3. Diagnosis of minor ischemic stroke, or Transient Ischemic Attack (TIA, defined as acute focal neurological deficits, with complete resolution of symptoms within 24 h of onset). In cases where onset time cannot be established, it will be considered to be the time when patient was last known to be well.
4. CT scan or MRI, with findings consistent with an ischemic etiology of symptoms.
5. Atrial Fibrillation (AF, paroxysmal or persistent), confirmed with ECG/Holter monitor, or by history (clinical documentation of previous AF must be provided).
6. Patients prescribed apixaban by their treating physician following their stroke/TIA.
7. Ability to obtain consent from patient or legally authorized representative.

Note: *The decision to treat with apixaban and the timing of the first dose will be determined by the attending physician, independent of the registry.* C*onsent to participate in the registry will be obtained only after the treating physician has made the decision to initiate apixaban therapy within 14 days of stroke/TIA.*

4.2 Exclusion Criteria

1. Acute or chronic renal failure, defined as eGFR <30 ml/min (Cockcroft Gault formula).
2. Known hypersensitivity to apixaban.
3. Prior treatment with apixaban or any other novel oral anticoagulant (including all Factor Xa antagonists). Treatment with warfarin prior to the stroke/TIA is acceptable, but enrolment cannot begin until the INR is ≤2.0.
4. Any significant ongoing systemic bleeding risk, i.e. active GI/GU bleeding or recent major surgery.
5. Any condition that, in the judgment of the investigator could impose hazards to the patient if study therapy is initiated or affect the participation of the patient in the study.
6. Recent past history or clinical presentation of ICH, subarachnoid haemorrhage (SAH), arterio-venous (AV) malformation, aneurysm, or cerebral neoplasm. At the discretion of each Investigator.
7. Hereditary or acquired haemorrhagic diathesis.
8. Stroke mimics (such as seizures, migraine etc.)
9. Contraindications to MRI, including metallic implants.

5.0 Treatment

Patients in whom apixaban is initiated within 14 days of TIA/stroke symptom onset will be included in the registry. The timing of initiation of therapy within that 14 day window will be determined by the treating physician. Patients fulfilling at least two of the following characteristics, will have received a reduced dose of ELIQUIS 2.5 mg twice daily: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 133 μmol/L (1.5 mg/dL). All other patients will have received a 5 mg dose to be taken orally twice daily.

6.0 Study Procedures and Evaluations

6.1 Screening/Baseline

The screening/baseline visit will be conducted within 24 hours of the initiation of apixaban in the patient as decided by their treating physician. All stroke patients will initially be screened with a non-contrast CT scan of the brain (standard of care).

Standard clinical assessments and data will be collected. This will include baseline National Institutes of Health Stroke Scale (NIHSS), Premorbid Modified Rankin Scale (mRS), Montreal Cognitive Score (MoCA) and vital signs, which will be recorded in a case report form. Past medical history and medications, baseline complete blood count, coagulation profile and renal function tests will also be recorded.

6.2 Imaging Procedures

6.2.1 MRI Study 1: Performed within 24 hours of recruitment

All MRI sequences will be completed in approximately 20 minutes. The MRI protocol will consist of a T1-weighted sagittal localizer, time of flight MRA and diffusion-weighted (DWI) and perfusion-weighted images (PWI; in patients without any contraindications to gadolinium contrast). Single shot Echoplanar (EPI) DWI images obtained using diffusion gradient strengths (b values) between 0 s/mm^2, equivalent to a T2-weighted image, and 1000 s/mm^2, applied in 3 orthogonal planes, will be obtained. The DWI acquisition parameters will be: repetition time (TR) of 3 s, spin echo time (TE) of 86 ms, 8 averages, 128x128 matrix base resolution zero filled to 256x256, 22 cm field-of-view, and 1396 Hz/pixel acquisition bandwidth. The entire brain will be imaged using 19 contiguous axial slices each 5 mm in thickness, with a 1.5 mm inter-slice gap.

6.2.2 MRI Study 2: Imaging studies repeated at day7 (±2 days)

All imaging sequences including susceptibility weighted imaging will be repeated at day 7 (±2 days) after enrolment, in order to assess for early asymptomatic hemorrhagic transformation.

In the event of any clinical deterioration, a repeat CT scan will be performed immediately. We hypothesize micro-hemorrhages may predict symptomatic bleeding. In addition, any supplemental brain imaging completed within the first 30 days after enrolment will be collected.

6.3 Clinical Follow-up Assessments

All patients will be followed for 90 days. This is the standard post-stroke assessment period (the majority of neurological and functional recovery occurs within this time frame). Patients will be assessed clinically at follow-up visits performed on Day 7(±2 days), and Day 90 (± 30 days) by a study team member (i.e. co-investigator, study coordinator). At each visit, vital signs will be noted, a comprehensive neurologic examination will be performed and mRS, NIHSS and MoCA

assessments will be conducted with the patient. Patients will be interviewed in detail to identify and ascertain any recurrent vascular event suggestive of a stroke or TIA. Work-up to determine the underlying etiology of stroke will be reviewed and any change in management plan will be recorded.

7.0 Statistics

The primary outcome will be tested with a single sample t-test. The null hypothesis is that the frequency of symptomatic hemorrhagic transformation is <2%. A convenience sample of 50 patients is planned initially. This will provide initial safety and feasibility data that can be used to plan future definitive studies as required. The primary efficacy analysis will be on an intention-to-treat basis.

8.0 Assessment of Adverse Events

8.1 Definition of Adverse Events

Adverse Event: An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Serious Adverse Event: A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability/incapacity, requires or prolongs patient hospitalization, is a congenital anomaly/birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Intensity of Adverse Event: The intensity of the AE should be judged based on the following:

1. Mild: the adverse event is temporary and easily tolerated by the subject;
2. Moderate: the adverse event causes the subject discomfort and interrupts the subject's normal activities.
3. Severe: the adverse event causes considerable interference with the subject's normal activities and may be incapacitating or life threatening including hospitalization or prolongation of hospitalization.

8.2 Adverse Event Reporting

Investigators will report serious adverse events (SAE), using standardized event, resolution and association codes. The SAE reporting period includes the entire study duration (3 months) and an additional week. All SAEs will be reported. Non-serious Adverse Events (AEs) unrelated to Apixaban treatment will not be reported.

9.0 Central Imaging Adjudication and Analysis

Dicom CT and MRI data will be transferred to the Stroke Imaging Laboratory at the University of Alberta for post-processing and analysis. All image assessments will be performed using software developed specifically for CT brain image analysis (Quantomo software package, Cybertrial Inc, Calgary, AB). The extent of any objective acute and chronic ischemic changes on all CT scans will be assessed using Alberta Stroke Program Early CT Scores (ASPECTS). The extent of subacute ischemic changes will also be assessed using the day 1 MRI (Diffusion-Weighted Imaging sequences). Infarct volumes will be measured objectively using planimetric techniques. The extent of periventricular leukoariosis will also be measured using planimetric techniques and an intensity threshold algorithm included in the Quantomo software package.

All cases of hemorrhagic transformation seen on post-dabigatran treatment scans will be graded using the ECASS (European Cooperative Acute Stroke Study) hemorrhage classification scheme:

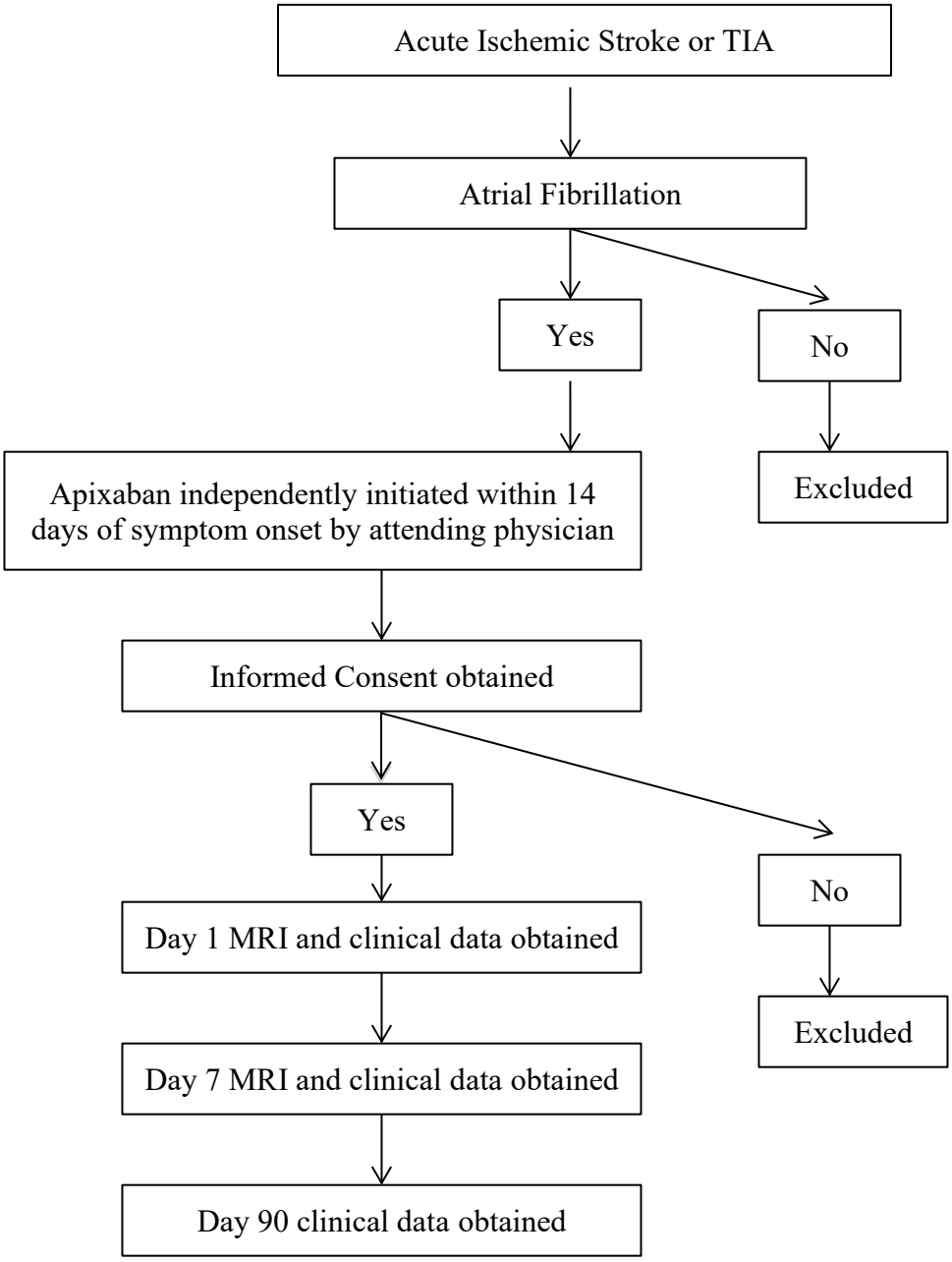
1. PH2 - parenchymal hemorrhage as a blood clot in more than 30% of the infarcted area with substantial space-occupying effect.
2. PH1 - parenchymal hemorrhage as blood clots in 30% or less of the infarcted area with some slight space-occupying effect.
3. HT2 - hemorrhagic transformation 2 - confluent petechiae within the infarcted area but no space-occupying effect.
4. HT1 - hemorrhagic transformation 1 – small petechiae along the margins of the infarct.
5. R - remote ICH, i.e. not topographically related to the infarct (most often in the contralateral hemisphere).

A symptomatic ICH (primary endpoint) will be defined as PH2, associated with an NIHSS deterioration of ≥4 points. The primary endpoint will be assessed using the day 7 MRI scan and any additional scans performed within 30 days of apixaban initiation.

10.0 Funding Source

This investigator-initiated study is funded by the Alliance. The funding will be used for MR imaging.

Figure 1: Algorithm



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