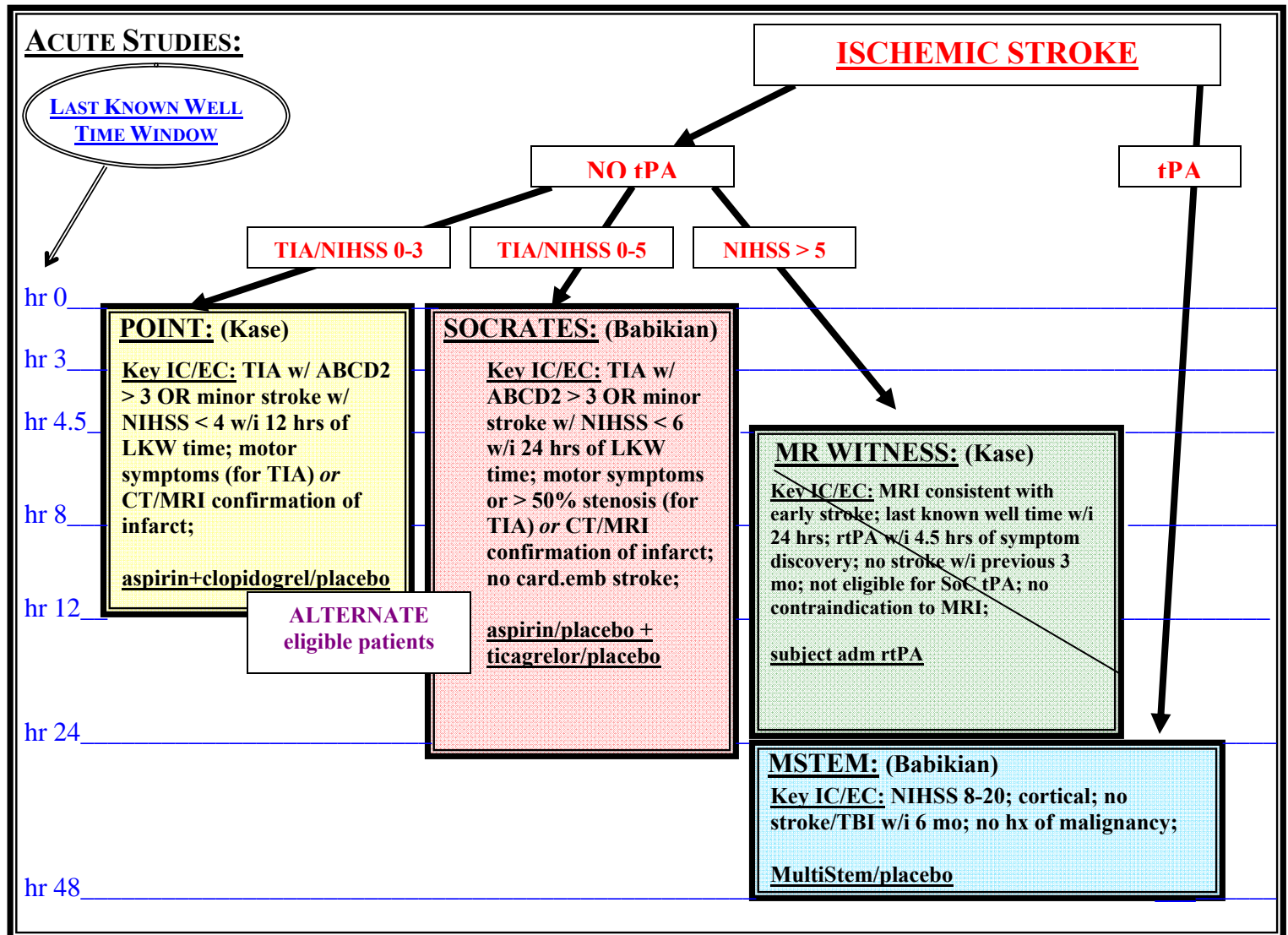


# Flowchart for Stroke Research 2014 (v9-3-2014)



**CONTACT:**

~ AFTER 4PM MON-FRI (TUDOR – CELL: 732-439-0876, PAGER 2644)  
 ~ SAT-SUN (HELENA – CELL: 508-982-0297; PAGER 5468)  
 ~ IF PAGING, PLEASE TEXT WHAT STUDY, YOUR NAME, AND CALL-BACK NUMBER.

**SUBACUTE STUDIES:**

**CAA: (Kase)**

**Key IC/EC:** age 55-90; probable CAA (Boston criteria) – 2+ lobar hemorrhages (macro or micro); no clinically significant deficits d/t CAA; MMSE > 25; no contraindication to MRI; no seizures w/i last 3 months

**Ponezumab/placebo**

**DALF: (Kase)**

**Key IC/EC:** age 18+; clinical evidence of a stable walking deficit d/t ischemic stroke (≥ 6 months ago); mRS of 1 to 3; ability to complete the 2MinWT and 10MWT; no hx of seizures, depression, baclofen or SSRI use; no UTI

**Dalfampridine/placebo**

**Navigate-ESUS: (Kase)**

**ESUS:** non-lacunar ischemic stroke; absence of extra- or intracranial atherosclerosis (50+%) in arteries of ischemic area; no cardioembolic source (ie. Afib); no other cause identified (e.g. arteritis, dissection, migraine/vasospasm, drug abuse)

**Rivaroxaban/placebo**

**MARISS: (Romero)**

**Key IC/EC:** Mild or rapidly improving acute ischemic stroke defined clinically: enroll after the determination to treat or not to treat w tPA; CT w/o hem or mass; age 18+; w/i 4.5 hrs LKW time; pre-hosp mRS 0-1

**Obs study**

# **POINT**

(NIH)

## **Inclusion Criteria:**

1. Neurologic deficit (based on history or exam) attributed to focal brain ischemia and either:
  - High-risk TIA: complete resolution of the deficit at the time of randomization and ABCD<sup>2</sup> score > 3; or
  - Minor ischemic stroke: residual deficit with NIHSS < 4 at the time of randomization
2. Ability to randomize within 12 hours of time last known well time free of new ischemic symptoms
3. Head CT or MRI ruling out hemorrhage or other pathology, such as vascular malformation, tumor, or abscess that could explain symptoms or contraindicate therapy
4. Ability to tolerate aspirin at a dose of 50-325 mg/day

## **Exclusion Criteria:**

1. Age < 18 years
2. TIA symptoms limited to isolated numbness, isolated visual changes, or isolated dizziness/vertigo
3. A candidate for thrombolysis, endarterectomy, or endovascular intervention
4. Receipt of any intravenous or intra-arterial thrombolysis within 1 week prior to index event
5. Gastrointestinal bleed or major surgery within 3 months prior to index event
6. History of nontraumatic intracranial hemorrhage
7. Clear indication for anticoagulation (eg, warfarin, heparin) anticipated during the study period (afib, mechanical heart valve, DVT, PE, antiphospholipid antibody syndrome, hypercoagulable state)
8. Qualifying ischemic event induced by angiography or surgery
9. Severe non-cardiovascular comorbidity with life expectancy < 3 months
10. Contraindication to clopidogrel or aspirin
11. Known allergy
12. Severe renal (serum creatinine > 2 mg/dL) or hepatic insufficiency (prior or concurrent diagnosis, with INR > 1.5, or any resultant complication, such as variceal bleeding, encephalopathy, or icterus)
13. Hemostatic disorder or systemic bleeding in the past 3 months
14. Current thrombocytopenia (platelet count <100 x10<sup>9</sup>/l) or neutropenia/granulocytopenia (<1 x10<sup>9</sup>/l)
15. History of drug-induced hematologic or hepatic abnormalities
16. Anticipated requirement for long-term (> 7 days) non-study antiplatelet drugs (e.g., dipyridamole, clopidogrel, ticlopidine), or NSAIDs affecting platelet function (such as prior vascular stent or arthritis)
17. Not willing or able to discontinue prohibited concomitant medications
18. Inability to swallow medications
19. At risk for pregnancy: premenopausal or post menopausal woman within 12 months of last menses without a negative pregnancy test or not committing to adequate birth control (e.g., oral contraceptive, two methods of barrier birth control, or abstinence)
20. Unavailability for follow-up
21. Inability to provide informed consent
22. Other neurological conditions that would complicate assessment of outcomes during follow-up
23. Ongoing treatment in another investigational therapy, or study treatment within the last 7 days

## **NOTES:**

- Get red POINT portfolio (near Judy's desk in 5W stroke room) for procedure.
- Call Helena Lau (508-982-0297) or Tudor Sturzoiu (732-439-0876) as soon as possible.
- For randomization: go to <https://webdcu.musc.edu/login.asp>; enter username and password; and add subject.
- Call POINT hotline (866-947-6468) with any questions.

# **SOCRATES**

## **(ASTRAZENECA)**

### **Inclusion Criteria:**

1. Provision of informed consent prior to any study specific procedures
2. Men or women  $\geq 40$  years of age
3. Either acute ischemic stroke or high-risk TIA as defined here and randomisation occurring within 24 hours after onset of symptoms:
  - A. Acute ischemic stroke
    - Neurological deficit attributed to the focal brain ischemia, and either of the following: – Persistent signs or symptoms of the ischemic event at the time of randomisation, OR – Acute, ischemic brain lesion documented by CT or MRI within 24 hours of onset of symptoms
    - NIHSS  $\leq 5$
  - B. High-risk TIA
    - Neurological deficit of acute onset attributed to focal ischemia of the brain by history or examination with complete resolution of the deficit, and at least one of the following: – ABCD2 score  $\geq 4$  and TIA symptoms not limited to isolated numbness, isolated visual changes, or isolated dizziness/vertigo;
    - Symptomatic intracranial arterial occlusive disease documented by TCD, ultrasound or vascular imaging, defined as at least 50% narrowing in diameter of a vessel that could account for the clinical presentation;
    - Documented internal carotid arterial occlusive disease, defined as at least 50% narrowing in diameter of a vessel that could account for the clinical presentation

### **Exclusion Criteria:**

1. Planned use of antithrombotic therapy in addition to study medication including antiplatelets (eg, open label ASA, GPIIb/IIIa inhibitors, clopidogrel, ticlopidine, prasugrel, dipyridamole, ozagrel, cilostazol) and anticoagulants (eg, warfarin, oral thrombin and factor Xa inhibitors, bivalirudin, hirudin, argatroban, unfractionated and LMWH). In addition, patients receiving or requiring dual antiplatelet therapy with ASA and P2Y12 inhibitors will be excluded.
2. Known hypersensitivity to ticagrelor or ASA
3. Any history of afib, ventricular aneurysm or suspicion of cardioembolic pathology for TIA or stroke
4. Planned carotid, cerebrovascular, or coronary revascularisation that requires halting study medication within 7 days of randomisation
5. Receipt of any IV or IA thrombolysis or mechanical thrombectomy within 24 hours prior to randomisation
6. Anticipated concomitant oral or IV therapy with strong cytochrome P450 3A (CYP3A) inhibitors or CYP3A substrates with narrow therapeutic indices that cannot be stopped for the course of the study:
  - Strong inhibitors: ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin (but not erythromycin or azithromycin), nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir;
  - CYP3A substrates with narrow therapeutic index: cyclosporine, quinidine, simvastatin at doses  $>40$  mg daily or lovastatin at doses  $>40$  mg daily
7. Anticipated requirement for long-term ( $>7$  days) non-steroidal anti-inflammatory drugs (NSAIDs)
8. Patients with known bleeding diathesis or coagulation disorder (eg, thrombotic thrombocytopenic purpura)
9. History of previous symptomatic non-traumatic intracerebral bleed at any time (asymptomatic microbleeds do not qualify), gastrointestinal (GI) bleed within the past 6 months, or major surgery within 30 days
10. Known severe liver disease (eg, ascites or signs of coagulopathy)
11. Renal failure requiring dialysis
12. Pregnancy or lactation
13. Involvement in the planning and/or conduct of the study (AstraZeneca staff and/or staff at the study site)
14. Inability of the patient to understand and/or comply with study procedures and/or follow-up, per Investigator
15. Previous enrolment or randomisation in the present study
16. Participation in another clinical study with an investigational product during the last 30 days

### **NOTES:**

- Get red SOCRATES portfolio (near Judy's desk in 5W stroke room) for procedure.
- Call Helena Lau (508-982-0297) or Tudor Sturzoiu (732-439-0876) as soon as possible.

# **MR WITNESS**

**(NIH/GENETECH)**

## **Inclusion Criteria:**

1. Age, 18 to 85 years inclusive
2. Brain MRI findings consistent with early stroke onset
3. Clinical diagnosis of acute ischemic stroke with disabling neurological deficit
4. Stroke symptoms present for at least 30 minutes with no significant improvement before treatment
5. Be last known well (without stroke symptoms) within 24 hours of triage
6. Be able to receive IV rt-PA within 4.5 hours from the time the symptoms were discovered.
7. MRI diagnostic of acute ischemic stroke and consistent with clinical syndrome
8. Time between completion of qualifying MRI studies to treatment initiation  $\leq 1$  hour

## **Exclusion Criteria:**

1. Symptoms rapidly improving or only minor before start of study drug
2. Severe stroke as assessed clinically (e.g., NIHSS score  $> 25$ ) or by appropriate imaging techniques (lesion volume  $> 1/3$  of MCA by visual inspection or  $> 100 \text{ cm}^3$  using the ellipsoid estimation formula of ABC/2)
3. Stroke or serious head trauma within the previous 3 months
4. Administration of heparin within the 48 hours preceding the onset of stroke, with an activated partial-thromboplastin time at presentation exceeding the upper limit of the normal range
5. Platelet count of less than 100,000 per cubic millimeter
6. Uncontrolled hypertension defined as systolic blood pressure  $> 185$  or diastolic blood pressure  $> 110$  that cannot be controlled except with continuous parenteral antihypertensive medication
7. Blood glucose less than 50 mg per deciliter or greater than 400 mg per deciliter
8. Symptoms suggestive of subarachnoid hemorrhage, even if CT/MRI scan was normal
9. Current oral anticoagulant treatment, regardless of INR. Intravenous t-PA can be considered for a patient with a history of recent dabigatran use if the history documents that the patient has not received dabigatran for  $> 24$  hrs AND if the patient has a normal creatinine AND also has an INR  $< 1.7$  and a PTT  $< 1.5 \times$  the average value of the normal range
10. Major surgery or severe trauma within the previous 3 months
11. Other major disorders associated with an increased risk of bleeding
12. Eligible for rt-PA therapy per institutional protocol as part of routine clinical practice
13. Non-ischemic etiology demonstrated by neuroimaging
14. Neuroimaging (CT or gradient echo MRI) evidence of acute or chronic ICH (non-microbleed)
15. Presence of 10 or more microbleeds on GRE (suggestive of amyloid angiopathy)
16. Any contraindication for MRI, e.g. presence of a pacemaker, ferromagnetic aneurysm clip, etc, premenopausal women with a positive pregnancy blood test, or severe claustrophobia.
17. Poor quality MRI - images are not interpretable
18. In the opinion of the investigator, the patient is not an appropriate candidate for IV rt-PA
19. Women known to be pregnant, lactating or having a positive or indeterminate pregnancy test

## **NOTES:**

- Procedure Forthcoming
- Call Helena Lau (508-982-0297) or Tudor Sturzoiu (732-439-0876) with any questions.



**Inclusion Criteria:**

1. Male or female subjects between 18 and 83 years of age, inclusive
2. Clinical diagnosis of cortical cerebral ischemic stroke
3. Occurrence of a moderate to moderately severe stroke with clear motor or speech deficit documented by NIHSS score of 8 to 20 (inclusive) that did not change by  $\geq 4$  points from the screening to the baseline assessment. The NIHSS score must be confirmed during the baseline visit 24 to 44 hours from the time of stroke onset. Note: The NIHSS screening score used for eligibility should be the last score collected prior to the baseline reconfirmation NIHSS score. There should be  $\geq 6$  hours between baseline and the last NIHSS assessment during screening.
4. Onset of stroke must have occurred 24 to 48 hours prior to administering the investigational product. Time of onset is defined as the time point when symptoms first began. For stroke that occurred during sleep, time of onset is defined as the time point when the subject was last observed to be normal or was self-reported to be normal.
5. Confirmation of acute hemispheric cortical infarct with brain MRI including DWI demonstrating an acute lesion measuring  $\geq 5$  mL and  $\leq 100$  mL
6. A Rankin score of 0 or 1, by either self-report or family report, prior to the current stroke
7. Subjects who received either tPA up to 4.5 hours post-stroke or underwent mechanical reperfusion according to the approved labels of tPA and the mechanical device, are eligible if they meet all eligibility criteria.
8. Female subjects who are either:
  - a. Not pregnant, not breastfeeding, and not planning on becoming pregnant during the study;
  - b. Not of childbearing potential, defined as one who has been postmenopausal for at least 1 year, or has been surgically sterilized, or has had a hysterectomy at least 3 months prior to the start of this trial;
  - c. If of childbearing potential, must agree to use an effective method of avoiding pregnancy to the end of the trial. Effective methods of avoiding pregnancy are contraceptive methods used consistently and correctly (including implantable contraceptives, injectable contraceptives, oral contraceptives, transdermal contraceptives, intrauterine devices, diaphragm with spermicide, male or female condoms with spermicide, or cervical cap), abstinence, or a sterile sexual partner
9. Male subjects with female partners of childbearing potential must agree to use adequate contraceptive methods (including a condom, plus 1 other form of contraception) if engaging in sexual intercourse.
10. Subjects or legal representatives must freely sign the informed consent form after the nature of the trial and the disclosure of his/her data has been explained.
11. Willing and able to comply with all aspects of the treatment and testing schedule
12. Willing and able to return to the trial site for the post-treatment evaluations

**Exclusion Criteria:**

1. Presence of a lacunar or a brainstem infarct on MRI as the etiology of current stroke symptoms
2. Reduced level of consciousness (score of  $>2$  for item 1a of NIHSS)
3. Occurrence of a hemorrhagic transformation of ischemic stroke as evidenced by computerized tomography (CT) or brain MRI scan that is clinically significant in the opinion of the investigator
4. Ipsilateral focal neurological deficits from prior lesions in the brain that would complicate evaluation
5. History of arrhythmias or QTc prolongation that is clinically significant in the opinion of the investigator
6. Experienced seizures since the onset of stroke
7. Experienced a major neurological event such as stroke or clinically significant head trauma within 6 months of screening
8. Uncontrolled hypertension, defined as persistent SBP $>220$  mmHg or DBP $>120$  mmHg, despite antihypertensive therapy
9. Blood glucose level  $<50$  mg/dL or  $>350$  mg/dL at baseline
10. Significant abnormal laboratory results at screening:
  - a.  $> 2$  x upper limit of normal (ULN) for alanine aminotransferase or aspartate aminotransferase;
  - b.  $> 1.5$  x ULN for total bilirubin;
  - c.  $> 2$  x ULN for serum creatinine; or
  - d. any other abnormal laboratory results at screening that are considered to be clinically significant in the opinion of the investigator

11. Subjects who have a significant comorbid medical condition(s), including, but not limited to:
  - a. severe kidney disease requiring hemodialysis or peritoneal dialysis;
  - b. advanced liver disease such as hepatitis or liver cirrhosis;
  - c. severe congestive heart failure or ejection fraction <30%;
  - d. severe lung disease requiring home oxygen; or
  - e. active unstable angina requiring daily treatment with nitrates or other medications
12. Known human immunodeficiency virus, ongoing systemic infection, severe local infection or who are immunocompromised
13. Have Alzheimer's disease or other dementias, Parkinson's disease, or any other neurological disorder that would affect their ability to participate in the trial or confound study assessments
14. Have a history of malignancy of any type, with the exception of adequately treated basal or squamous cell carcinoma of the skin
15. Have a contraindication for MRI such as implanted pacemakers or other metallic prosthesis incompatible with MRI, body weight, or claustrophobia
16. Have thrombocytopenia (platelet count <75,000/mm<sup>3</sup>) or heparin-induced thrombocytopenia
17. Have a life expectancy less than 90 days
18. Have a known allergy or religious objections to human tissue or bovine or porcine products
19. Prior participation in any other trial involving investigational pharmacological agents or devices within 30 days prior to investigational product infusion or planned participation in investigational rehabilitation stroke recovery program
20. Other serious medical or psychiatric illness that is not adequately controlled and, in the investigator's opinion, would not permit the subject to be managed according to the protocol
21. Previous surgical removal of the spleen
22. Major fluctuation in neurological status since the onset of stroke indicating progression or expansion of stroke or possible transient ischemic attack
23. Plan to have a neurovascular procedure (eg, carotid endarterectomy, stent placement, etc.) within the first year following stroke

#### **NOTES:**

- Get blue Athersys MultiStem binder (near Judy's desk in 5W stroke room) for procedure.
- Call Helena Lau (508-982-0297) or Tudor Sturzoiu (732-439-0876) as soon as possible.

# **A9951024 (Pfizer Ponezumab)**

## **(PFIZER)**

### **Inclusion Criteria:**

1. Men, and women of non-childbearing potential between the ages of 55 and 90 years old who have the diagnosis of probable CAA using the Boston criteria and have an acceptable sMRI in the previous 12 months for review. Male subjects must agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned drug. Female subjects who are not of childbearing potential (ie, meet at least one of the following criteria): (a) Have undergone hysterectomy or bilateral oophorectomy; (b) Have medically confirmed ovarian failure; or (c) Are medically confirmed to be post-menopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; with laboratory confirmation).
2. CAA disease has not resulted in any meaningful clinical cognitive or functional deficit as documented by the PI in consultation with the sponsor.
3. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the trial.
4. Subjects are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures.
5. In general good health, in the opinion of the Principal Investigator (PI), based on medical history, physical examination, vital signs, 12-lead ECG, and laboratory values, including hematology and chemistry values.
6. Subjects must have corrected vision at or better than 20/50 as assessed with a Snellen chart. If glasses are required to meet these criteria, they must be MRI-compliant glasses provided by the site.
7. An acceptable screening fMRI that passes QC requirements.

### **Exclusion Criteria:**

1. Co-morbid diagnosis of clinically documented Alzheimer's disease or significant cognitive impairment. A score of < 26 on the MMSE.
2. History of cancer within the last 5 years (except for cutaneous basal cell, squamous cell cancer resolved by excision, colon polyp resolved by excision, or non-progressive prostate cancer per investigator's judgment).
3. History of clinically significant (as determined by the PI) cardiac arrhythmia or heart block (eg sick sinus syndrome, ventricular tachycardia or fibrillation, sustained supraventricular tachycardia, symptomatic bradycardia, congenital long QT interval syndrome, atrial fibrillation).
4. History or diagnosis of clinically significant (as determined by the PI) ischemic heart disease (eg, angina, clinically significant coronary artery disease, myocardial infarction in the past 2 years), congestive heart failure, cardiomyopathy, myocarditis, left ventricular hypertrophy, valvular heart disease.
5. History of clinically significant (as determined by the PI) renal disease, such as glomerulonephritis, nephrotic syndrome, single kidney or polycystic kidney.
6. Subjects with uncontrolled hypertension (>170/100).
7. History of clinically significant (as determined by the PI) syncope, head trauma, or clinically significant unexplained loss of consciousness within the last 5 years.
8. A diagnosis of major depressive disorder or other psychiatric illness as the primary diagnosis per the DSM-IV TR criteria per the investigator's judgment.
9. History of schizophrenia, bipolar disorder, or other severe mental illness.
10. Known history of alcohol or drug abuse (as defined by the DSM-IV-TR) within 5 years prior to dosing or a positive result as a result of illicit drugs on the drug screening test.
11. Known positive HIV status.
12. Subjects who reside in a nursing home or that are inpatients in a hospital.
13. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
14. Pregnant females; breastfeeding females; females of childbearing potential; males of childbearing potential not using highly effective contraception or not agreeing to use highly effective contraception for at least 28 days after last dose of investigational product; males of childbearing potential not using two (2) methods of highly effective contraception or not agreeing to use two (2) methods of highly effective contraception for at least 28 days after last dose of investigational product.
15. Subject's body weight cannot exceed 105 kg.

### **Exclusions Related to Medications or Procedures**

1. Previous exposure to investigational or non-investigational immune- or biologic therapies for Alzheimer's disease such as anti-A $\beta$  antibodies, or  $\alpha$ - or  $\gamma$ -secretase inhibitors.
2. Any contraindications to MRI such as, but not limited to cardiac pacemaker; implanted cardiac defibrillator; aneurysm clips; carotid artery vascular clamp; neurostimulator; insulin or infusion pumps; implanted drug infusion device; bone growth/fusion stimulator; cochlear, otologic, ear implant; severe claustrophobia or requiring sedation; passive implants that may be weakly ferromagnetic in the vicinity of the RF coil that may cause image artifacts in the head scans; obesity or body habitus that exceeds MRI table weight limits or prevents subject from fitting into the scanner.
3. History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody or IgG-fusion protein.
4. Medications that may negatively affect cognitive function, such as anticholinergics (including agents with pronounced anticholinergic properties such as amitriptyline with the following caveats: (a) Sedatives and tranquilizers (eg, benzodiazepine and non-benzodiazepine hypnotics) used as a sleeping aid and taken routinely are allowable provided that subjects have been on a stable dose for at least 60 days prior to dosing; (b) Anti-epileptic drugs for reasons other than seizures are permitted provided that subjects have been on a stable dose for at least 60 days prior to dosing. Topiramate and barbiturates are excluded.
5. The following medications are excluded if used from **1 month** prior to the Screening visit through the end of the study: (a) Anti-coagulants; (b) Approved cognitive enhancers (cholinesterase inhibitors, memantine).
6. The use of anti-inflammatory (NSAIDs and steroids) drugs prescribed specifically/solely for treatment of CAA (other stable use permitted).
7. Subjects cannot participate in other clinical drug trials for the duration of the study. Subject may not donate blood within 8 weeks prior to drug infusion and for 6 months after study drug administration.
8. History of sensitivity to heparin or heparin-induced thrombocytopenia.

### **Exclusions Related to Findings on Screening Tests**

1. Clinically significant laboratory abnormalities in the opinion of the Investigator or Sponsor.
2. Screening creatinine clearance of <30 mL/min for CAA subjects. Creatinine clearance of 30-49 mL/min will require the Investigator to ensure that the subject has no clinically significant renal disease that would impact participation in the trial.
3. Active infection with hepatitis B or positive Hepatitis C screening labs.
4. A clinically significant (as determined by the PI) abnormality evident on the Screening, the 12-lead ECG, including complete heart block, bradycardia (heart rate <40 beats/minute), sinus pauses >2 seconds, second or third degree heart block, QTc >470 for males >480 or for females or other abnormalities judged clinically significant by the PI.
5. Any other condition, which in the opinion of the PI in consultation with the sponsor, would put the subject at increased safety risk or otherwise make the subject unsuitable for this study. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
6. Unwilling or unable to comply with the Life Style Guidelines described in this protocol.
7. Subjects with vision impairments that cannot be corrected in the scanner (i.e. using MRI compatible lenses) that would prevent them from performing the visual fMRI task.

### **NOTES:**

- Call Helena Lau (508-982-0297) or Tudor Sturzoiu (732-439-0876) with questions or referrals.



# **DALF** **(ACORDA)**

## **Inclusion Criteria:**

1. Men or women aged 18 or older
2. Clinical evidence of a stable walking deficit due to an ischemic stroke, as judged by the Investigator, based on review of medical records and physical exam. Such deficit was not present prior to the stroke and cannot be attributed primarily to other conditions (e.g. chronic obstructive pulmonary disease, arthritis). Evidence of walking deficits is objectively supported by any one of the following findings on clinical examination:
  - obvious slowness of movement assigned primarily to the stroke
  - use of an assistive walking device such as a cane or walker
  - Presence of movement pattern deviations such as stiff-legged gait, foot drop, hip hiking and hip circumduction
3. Modified Rankin Scale score of 1 – 3, regardless of the cause(s) of the disability
4. Sufficient ambulatory ability to independently complete the 2MinWT and 10MWT
5.  $\geq 6$  months from occurrence of most recent stroke.
6. All men and women of childbearing potential must agree to practice a highly effective method of birth control (have a failure rate of  $\leq 1\%$ ) during the study and until 3 months after their last dose of investigational product. Women of childbearing potential must have a negative urine pregnancy test prior to study enrollment.
7. Body mass index (BMI) ranging between 18.0 to 35.0 kg/m<sup>2</sup>
8. Adequate cognitive ability to provide informed consent, as determined by the Investigator

## **Exclusion Criteria:**

1. Woman who is not surgically sterile or is less than 2 years postmenopausal, and does not agree to use a highly effective birth control method during the study and up to 3 months after the last dose of study drug.
2. Woman who is pregnant, breastfeeding, or planning to become pregnant
3. History of seizures, except simple febrile seizures
4. Moderate or severe renal impairment as defined by a calculated creatinine clearance of  $\leq 50$  mL/minute using the Cockcroft-Gault Equation
5. An abnormal laboratory value that, in the Investigator's judgment, is both clinically significant and has the potential to affect the subject's ability to safely complete the study
6. Diagnosis of multiple sclerosis
7. Unstable angina, uncontrolled hypertension, moderate or severe heart failure (NYHA class III and IV) or any other significant abnormality that, in the opinion of the investigator, poses an undue risk for the subject's participation in the study.
8. Severe depression as indicated by a score of  $\geq 30$  on the Beck Depression Inventory (BDI)
9. Suicide attempt within 1 year prior to the Screening Visit, or severe suicidal ideation within 6 months prior to the Screening Visit (i.e., the subject answers Yes to Questions 4 or 5 in the Screening C-SSRS), or subject is at significant risk of suicidal behavior in the opinion of the Investigator.
10. History of drug or alcohol abuse within the past year.
11. Any other medical condition, per Investigator's judgment, that would interfere with the conduct of the study or interpretation of study results.
12. Previous use of AMPYRA, dalfampridine, fampridine or 4-aminopyridine (4-AP).
13. Initiation or change of a prescription medication regimen or therapy within 4 weeks prior to the Screening Visit, or concomitant medication or concomitant therapy is expected to change during the course of the study
14. Initiation of baclofen or tizanidine within 4 weeks prior to the Screening Visit or any change in dosing regimen within 4 weeks prior to the Screening Visit
15. Initiation of a serotonin reuptake inhibitor (SSRI) within 3 months prior to the Screening Visit, or any change in dosing regimen within 3 months prior to the Screening Visit
16. Botulinum toxin use within 2 months prior to the Screening Visit
17. Orthopedic surgical procedures in any of the extremities within the past 6 months
18. Participation in an investigational interventional trial within 4 weeks prior to the

## **NOTES:**

- If you see potential patients in clinic, please refer (email name & MRN) to Helena & initiate conversation about study with patient.

# **MaRISS**

(AHA funded)

## **ELIGIBILITY CRITERIA**

Patients will be invited to participate in this research registry study **after** the decision to treat stroke with IV rtPA or not has been already made by the attending physician and patients have received the recommended standard of care acute treatment.

### **Inclusion criteria:**

1. Patients with mild or rapidly improving acute ischemic stroke defined clinically. MaRISS does not define Mild Stroke or Rapidly Improving Stroke for purposes of enrollment. It enrolls patients after the determination to treat or not to treat has been made, in order not to influence treatment decisions.
2. Absence of non-ischemic conditions neuro-imaging (i.e. absence of hemorrhage or a masson non-contrast brain CT, or more advanced imaging obtained according to participating site's imaging protocol).
3. Age 18 years or older.
4. Arrival to the hospital within 4.5 hours after the onset of stroke symptoms.
5. Willing to provide consent.
6. Available by telephone and willing to receive two follow-up telephone calls over the next 3 months.

### **Exclusion Criteria:**

1. Acute stroke patients arriving to the hospital beyond 4.5 hours from symptom onset.
2. Unable to obtain consent from either patient or legally authorized representative.
3. Pre-morbid modified Rankin scale greater than 1.
4. Not available by telephone.

**Definition for mild or rapidly improving stroke:** Traditionally, the NIHSS has been used to describe a severity of a stroke. Most recent clinical studies of intervention for acute ischemic stroke have excluded those with an NIHSS <5 or <6. However, in clinical practice, the determination of mild stroke as a reason not to administer IV rtPA is left up to the clinician. Amongst 10,295 GWTG-S patients not treated with IV rtPA solely because of a mild stroke, 94% had a NIHSS of 5 or less. However, it is clear that an isolated aphasic syndrome, even though it would accrue a low NIHSS, would be quite disabling and would not be considered mild.

A recent consensus statement recommended defining rapidly improving stroke symptoms as those that improve to an NIHSS <5 and are non-disabling. However, a large proportion of the improvement may occur prior to hospital arrival. Although a number of EMS scales of severity are available, they have not been carefully analyzed to include pre-hospital fluctuations in the definition of rapidly improving stroke. Therefore, in practice, the physician ascertains if symptoms have rapidly improved or not. In GWTG-S, amongst those not treated due to only rapidly improving symptoms, 26% had an NIHSS >5 suggesting persistent disabling symptoms. Rapid improvement would suggest rapid recanalization and reperfusion of ischemic tissue, while mild strokes are probably caused by persistent occlusion of a vessel. In a retrospective analysis of GWTG-S, rapidly improving stroke patients tended to be older, have more cardiac and carotid disease, and have a higher NIHSS at baseline. After adjustment for multiple variables, rapidly improving strokes that improve to mild had the best outcomes.

### **Notes:**

- Tudor will screen daily Monday-Friday; and we will take care of consenting, 3 hospital evaluations, and the 2 phone follow-ups.
- The TOAST criteria determination will be done by Dr. Rafael Romero at some point before discharge (or data entry).

# **NAVIGATE-ESUS**

(BAYER)

Secondary stroke prevention trial designed to evaluate the safety & efficacy of Rivaroxaban as a secondary stroke prevention therapy in patients who have suffered an embolic stroke of undetermined source (ESUS).

- ESUS is defined as: non-lacunar ischemic stroke detected by CT or MRI; absence of extracranial/intracranial atherosclerosis causing 50%+ stenosis in arteries supplying the area of recent brain ischemia; no major risk cardioembolic source of embolism (e.g. atrial fibrillation); no other specific cause of stroke identified (e.g. arteritis, dissection, migraine/vasospasm, drug abuse)