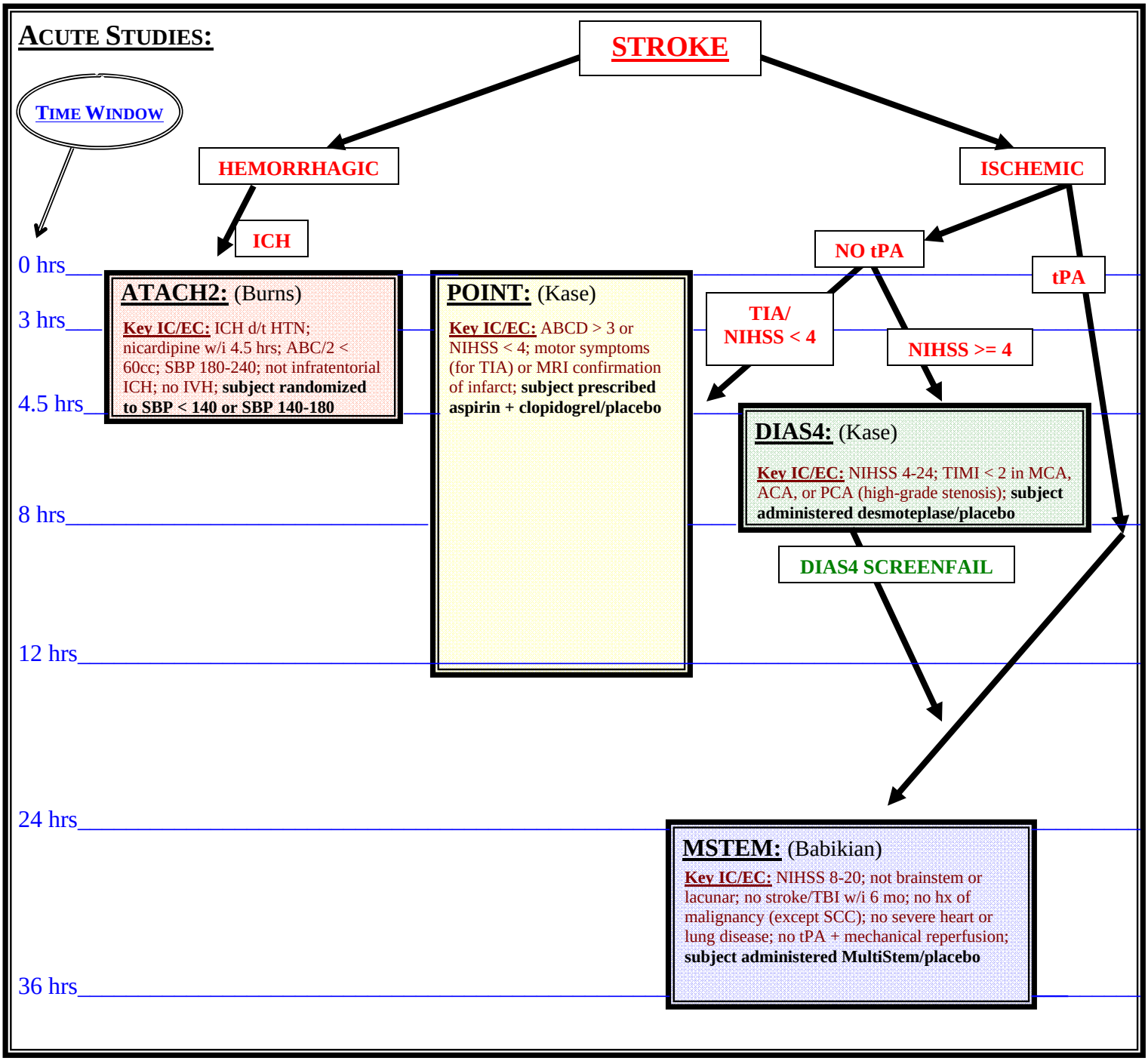
FLOWCHART FOR STROKE RESEARCH 2013 (1.0)

ACUTE STUDIES:



CONTACT: → ~ AFTER 5PM MON-FRI (HELENA – CELL: 508-982-0297);
~ SAT-SUN (CHRIS – CELL: 781-929-7863; HOME: 781-536-4011; PAGER 2644)

SUBACUTE STUDIES:

ARUBA: (Nguyen)

Key IC/EC: unruptured BAVM diagnosed by MRI/MRA, CTA, or angiogram; no prior hemorrhage, AVF, or fistulae; **subject randomized to intervention/medical management**

DALF: (Pikula)

Key IC/EC: stable sensorimotor deficit d/t ischemic stroke; 6 mo post stroke; no hx of seizures; no baclofen; no SSRI or depression; no UTI; **subject prescribed dalfampridine/placebo**

ATACH2

Inclusion Criteria:

1. Age 18 years or older
2. Patient can be randomized within 4.5 hours of symptom onset.
3. IV nicardipine can be initiated within 4.5 hours of symptom onset.
4. Clinical signs consistent with the diagnosis of stroke, including impairment of language, motor function, cognition, and/or gaze, vision, or neglect
5. Total GCS score (aggregate of verbal, eye, & motor response scores) of 5 or greater at enrollment
6. CT scan demonstrates intraparenchymal hematoma with manual hematoma volume measurement <60 cc.
7. INR value < 1.5
8a. For subjects randomized prior to IV antihypertensive administration: SBP greater than 180 mmHg* prior to IV antihypertensive treatment (this includes pre-hospital treatment) and without spontaneous SBP reduction to below 180 mmHg at the time of randomization
8b. For subjects randomized after IV antihypertensive administration: SBP greater than 180 mmHg prior to IV antihypertensive treatment (this includes pre-hospital treatment) and without SBP reduction to below 140 mmHg at the time of randomization
9. Signed and dated informed consent by subject or legally authorized representative

** Note: Patients with SBP < 180 should be monitored for 4.5 hours from symptom onset as their SBP may rise to eligible levels before the eligibility window closes.*

Exclusion Criteria:

1. Time of symptom onset cannot be reliably assessed.
2. Previously known neoplasms, AVM, or aneurysms
3. Intracerebral hematoma considered to be related to trauma
4. ICH located in infratentorial regions such as pons or cerebellum
5. IVH associated with intraparenchymal hemorrhage and blood completely fills one lateral ventricle or more than half of both ventricles
6. Subject considered a candidate for immediate surgical intervention by the neurosurgery service
7. Pregnancy or parturition within previous 30 days or active lactation
8. Any history of bleeding diathesis or coagulopathy
9. Use of dabigatran within the last 48 hours
10. A platelet count less than 50,000/mm3
11. Known sensitivity to nicardipine
12. Pre-morbid disability requiring assistance in ambulation or activities of daily living
13. Subject's living will precludes aggressive ICU management
14. Subject is currently participating in another interventional clinical trial

NOTES:

- Get white ATACH2 study binder (near Judy's desk in 5W stroke room) for procedure.
- Call Helena Lau (508-982-0297) or Chris Carr (781-929-7863) as soon as possible.
- For randomization: go to https://dcu.musc.edu/atach2/; enter username and password; and add subject.
- Call ATACH2 hotline (612-347-5710) with any questions.

DIAS4

Inclusion Criteria:

1. Clinical diagnosis of acute ischemic stroke
2. Informed consent/HIPAA authorisation has been obtained according to a procedure approved by the ethics committee responsible for approval of the study at this site.
3. Male or female between 18 and 85 years of age
4. Treatment of the subject can be initiated within 4.5 - 9 hours after the onset of stroke symptoms. If the actual time of onset of stroke is unclear, then the onset will be considered the time that the subject was last known to be well. All measures are to be taken so treatment with alteplase within 4.5 hours of symptom onset is not delayed in subjects who qualified for receiving alteplase.
5. The subject has a score of 4 - 24 on the NIHSS with clinical signs of hemispheric infarction (for example, hemiparesis).
6. The subject must receive IMP within 60 minutes after completion of diagnostic imaging screening. The time stamp on the last imaging sequence is the reference for calculating the time elapsing.
7. The subject shows occlusion or high-grade stenosis as assessed by an MRA or CTA in proximal cerebral arteries that corresponds to the acute clinical deficit. Eligible vessels are the middle cerebral artery (MCA M1, MCA M2), anterior cerebral artery (ACA) or posterior cerebral artery (PCA). Patients presenting with subtle or slight hyperintensity on FLAIR in the region of DWI lesion can be randomized according to the protocol. Patients presenting with patterns of less acute infarction within the territory of the obstructed artery, e.g. with cortical hemorrhagic transformation or contrast enhancement, having a clearly demarcated infarction on FLAIR, must not be randomized.

Exclusion Criteria:

1. The subject has a pre-stroke mRS score of greater than 1, indicating previous disability.
2. The subject has previously been exposed to desmoteplase.
3. The subject has participated in any investigational study in the past 30 days.
4. The subject has a terminal illness with a life-expectancy of less than 6 months.
5. In the opinion of the investigator, the subject has any condition that could impose hazards to the subject, if study therapy is initiated, or affect the participation of the subject in the study (for example, subject with metastatic cancer or with severe microangiopathy such as hemolytic uremic syndrome or thrombotic thrombocytopenic purpura).
6. Consciousness level greater than 2 on question 1a of NIHSS
7. The subject has a history or clinical presentation of ICH, subarachnoid hemorrhage (SAH), arterio-venous malformation, aneurysm, or cerebral neoplasm. Subjects with incidental small intracranial aneurysm can be considered for the study if the aneurysm is greater than 5 mm, not thrombosed, and not visibly bleeding.
8. The subject has symptomatic acute vertebral or basilar artery occlusion.
9. The subject is on oral anticoagulants and has a prolonged prothrombin time (INR greater than 1.6).
10. The subject has been treated with heparin in the past 48 hours and has a prolonged partial thromboplastin time exceeding the upper limit of the local laboratory normal range. Preventive low doses of LMWH (for example, for deep vein thrombosis (DVT) prophylaxis) do not disqualify the subject from the study.
11. The subject has been treated with glycoprotein IIb - IIIa inhibitors within the past 72 hours. Use of single agent oral platelet inhibitors (e.g. low-dose clopidogrel 75 mg or low-dose aspirin <= 325 mg) or the combination of low-dose-aspirin (e.g. 50 mg) and dipyridamole (e.g. 400 mg) prior to study entry is permitted.
12. The subject in the past 72 hours has been treated with factor Xa inhibitors, direct thrombin inhibitors, or any anticoagulants other than those specified in exclusion criteria 9 and 10.
13. The subject has a baseline platelet count less than 100,000 cells/µL.
14. The subject has a baseline haematocrit of less than 0.25.
15. The subject has a baseline blood glucose less than 50 mg/dL or greater than 200 mg/dL (less than 3 mmol/L or greater than 11 mmol/L). Subjects with blood glucose value between 200-300 mg/dL can be considered for the study only if the blood glucose value decreases to less than 200 mg/dL after antidiabetic treatment and before administration of IMP.
16. The subject has uncontrolled hypertension defined as a blood pressure greater than 185 mmHg systolic or greater than 110 mmHg diastolic immediately prior to IMP administration or requiring aggressive treatment to reduce the blood pressure within the limits. The definition of aggressive treatment is left to the discretion of the investigator.

17. The subject has a hereditary or acquired hemorrhagic diathesis.
18. The subject has had a gastrointestinal or urinary bleeding within the past 21 days.
19. The subject has had an arterial puncture at a non-compressible site within the past 7 days.
20. The subject has had another stroke or a serious head injury in the past 6 weeks.
21. The subject has had major surgery within the past 14 days.
22. The subject has had seizure at the onset of stroke.
23. The subject has had an acute myocardial infarction (AMI) within the past 3 weeks.
24. The subject has been treated with a thrombolytic agent within the past 72 hours.
25. The subject is a pregnant woman (positive serum βHCG pregnancy test, positive urine pregnancy test or clinically evident pregnancy).
26. The subject is, in the opinion of the investigator, unlikely to comply with the clinical study protocol or is unsuitable for any other reason.
27. The subject shows signs of extensive early infarction on MRI or CT in any affected area that is an infarcted core involving >1/3 of MCA territory or > 1/2 of the ACA or PCA territories.
28. The subject has imaging evidence of ICH or SAH (regardless of age of the bleeding); Arterio-Venous malformation; cerebral aneurysm; or cerebral neoplasm (incidental meningioma and microbleeds per se are not exclusion criteria. An incidental intracranial aneurism that is small (< 5 mm), not thrombosed, and not visibly bleeding is not an exclusion criterion).
29. The subject has well developed parenchymal hyperintensity on FLAIR, T2*, or EPI-T2 images, or marked hypodensity on CT, indicative of subacute infarction, or enhancement with morphologic features suggesting the lesion is more than 9 hours old.
30. The subject has an internal carotid artery occlusion on the side of the stroke lesion.
31. The subject has a contraindication to the imaging technique (that is, ferromagnetic objects for MRI, contraindications to contrast agent, etc. Refer to the Imaging Manual for contraindications to imaging technique).
32. The subject has any intracranial pathology that would interfere with the assessment of the chosen imaging technique for screening.

NOTES:

- Get green clipboard inside green DIAS4 briefcase (near Judy's desk in 5W stroke room) for procedure.
- Call Helena Lau (508-982-0297) or Chris Carr (781-929-7863) as soon as possible.
- For randomization: go to: www.clinphone.com/signin; click on "Enter My ClinPhone Online"; enter username and Password; click on "IWR Study Access (Investigator 64003)"; enter PIN; and proceed through randomization module.
- Call DIAS4 hotline (866-795-0159) with any questions.

POINT

Inclusion Criteria:

1. Neurologic deficit (based on history or exam) attributed to focal brain ischemia and either:
- **a.** High-risk TIA: complete resolution of the deficit at the time of randomization and $ABCD^2$ score > 4; or:
- **b.** Minor ischemic stroke: residual deficit with NIHSS < 3 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. In the judgment of the treating physician, 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 (atrial fibrillation, mechanical heart valve, deep venous thrombosis, pulmonary embolism, 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 x109/l) or neutropenia/granulocytopenia (<1 x109/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 study of an investigational therapy, or treatment in such a study 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 Chris Carr (781-929-7863) 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.

MSTEM

Inclusion Criteria:

1. Male or female subjects between 18 and 79 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 National Institutes of Health Stroke Scale (NIHSS) score of 8 to 20 (inclusive) that did not change by ≥4 points from the screening to the baseline assessment. The NIHSS score must be confirmed during the baseline visit 24 to 32 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 ≥6 hours between baseline and the last NIHSS assessment during screening.
4. Onset of stroke must have occurred 24 to 36 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 magnetic resonance imaging (MRI) including diffusion-weighted imaging demonstrating an acute lesion measuring ≥5 mL and ≤100 mL
6. A Rankin score of 0 or 1, by either self-report or family report, prior to the onset of symptoms of the current stroke
7. Subjects who received either tissue plasminogen activator (tPA) up to 4.5 hours post-stroke, or underwent mechanical reperfusion 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 systolic blood pressure >220 mmHg or diastolic blood pressure >120 mmHg, despite antihypertensive therapy
9. Blood glucose level <50 mg/dL or >350 mg/dL at baseline
10. Abnormal laboratory results at screening that are considered to be clinically significant in the opinion of the investigator
11. Known history of severe congestive heart failure or history of ejection fraction <30%
12. Active unstable angina requiring daily treatment with nitrates or other medications
13. Known human immunodeficiency virus, ongoing systemic infection, severe local infection or who are immunocompromised

14. Have other neurological disorders such as Alzheimer's disease, Parkinson's disease, or other degenerative disease that would affect their ability to participate in the trial or complicate evaluation
15. Have a history of malignancy of any type, with the exception of adequately treated basal or squamous cell carcinoma of the skin
16. Have severe lung disease requiring home oxygen
17. Have a contraindication for MRI such as implanted pacemakers or other metallic prosthesis, body size, or claustrophobia
18. Have thrombocytopenia (platelet count <75,000/mm3) or heparin-induced thrombocytopenia
19. Have a life expectancy less than 90 days
20. Have a known allergy or religious objections to human tissue or bovine or porcine products
21. 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
22. 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
23. Previous surgical removal of the spleen
24. Plan to have a neurovascular procedure (eg, carotid endarterectomy, stent placement, etc.) within the first year following stroke
25. Received both tPA and mechanical reperfusion for the current stroke

NOTES:

- Procedure forthcoming (as of 1/28/2013)
- Call Helena Lau (508-982-0297) or Chris Carr (781-929-7863) with any questions.

ARUBA

Inclusion Criteria:

1. Patient must have unruptured BAVM diagnosed by MRI/MRA, CTA and/or angiogram.
2. Patient must be 18 years of age or older.
3. Patient must have signed Informed Consent, Release of Medical Information, and Health Insurance Portability and Accountability Act (HIPPAA/U.S. only) Forms.

Exclusion Criteria:

1. Patient has BAVM presenting with evidence of recent or prior hemorrhage.
2. Patient has received prior BAVM therapy (endovascular, surgical, radiotherapy).
3. Patient has BAVM deemed untreatable by local team, or has concomitant vascular or brain disease that interferes with/or contraindicates any interventional therapy type (stenosis/occlusion of neck artery, prior brain surgery/radiation for other reasons).
4. Patient has baseline Rankin greater than or equal to two.
5. Patient has concomitant disease reducing life expectancy to less than 10 years.
6. Patient has thrombocytopenia (less than 100,000/uL).
7. Patient has uncorrectable coagulopathy (INR greater than 1.5).
8. Patient is pregnant or lactating.
9. Patient has known allergy against iodine contrast agents.
10. Patient has multiple-foci BAVMs.
11. Patient has any form of arteriovenous or spinal fistulas.

Previous diagnosis of any of the following:

12. Patient has a diagnosed Vein of Galen type malformation.
13. Patient has a diagnosed cavernous malformation.
14. Patient has a diagnosed dural arteriovenous fistula.
15. Patient has a diagnosed venous malformation.
16. Patient has a diagnosed neurocutaneous syndrome such as cerebro-retinal angiomatosis (von Hippel-Lindau), encephalo-trigeminal syndrome (Sturge-Weber), or Wyburn-Mason syndrome.
17. Patient has diagnosed BAVMs in context of moya-moya-type changes.
18. Patient has diagnosed hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber).

NOTES:

- Subacute study
- Call Helena Lau (508-982-0297) or Chris Carr (781-929-7863) with any questions.

DALF

Inclusion Criteria:

1. History of a stable sensorimotor deficit due to an ischemic stroke, as confirmed by the Investigator with supportive prior imaging findings (MRI/ CT scan) or imaging report
2. ≥ 6 months post-stroke
3. Men or women aged 18 to 85 years inclusive
4. Have a body mass index (BMI) ranging between 18.0 – 35.0 kg/m, inclusive
5. No previous use of AMPYRA, dalfampridine, fampridine or 4-aminopyridine (4-AP)
6. Have sufficient ambulatory ability to complete T25FW at Screening Visit and every other visit as required
7. Lower extremity motor Fugl-Meyer Assessment score of ≤27
8. Adequate cognitive ability to provide informed consent, as determined by the Investigator
9. Sexually active men must agree to use a barrier method of contraception and/or have a female partner who uses an effective method of contraception.

Exclusion Criteria:

1. Sexually active woman of childbearing potential who is not surgically sterile, less than two years postmenopausal, or not using an effective birth control method
2. Pregnant or breastfeeding
3. History of seizures, except simple febrile seizures
4. Moderate or severe renal impairment as defined by a calculated creatinine clearance of ≤ 50 mL/minute using the Cockcroft-Gault Equation
5. Evidence of an active urinary tract infection (UTI) at the Screening Visit or within the 2 weeks prior to the Screening Visit
6. Initiation or change of a prescription medication regimen or therapy within 4 weeks prior to the Screening Visit, and/or concomitant medication regimen or concomitant therapy is expected to change during the course of the study
7. 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
8. 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
9. Botulinum toxin use within 2 months prior to the Screening Visit
10. Orthopedic surgical procedures in any of the extremities within the past 6 months
11. Unstable angina, uncontrolled hypertension or any other significant cardiovascular abnormality as deemed by the Investigator
12. Severe depression as indicated by a score of ≥30 on the Beck Depression Inventory (BDI)
13. History of drug or alcohol abuse within the past year
14. 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
15. Diagnosis of multiple sclerosis
16. Any other medical condition, per Investigator's judgment, that would interfere with conduct of study or interpretation of study result
17. Participation in an investigational interventional trial within four weeks prior to Screening Visit

NOTES:

- Subacute study
- Call Helena Lau (508-982-0297) or Chris Carr (781-929-7863) with any questions.