Platelet-Oriented Inhibition in New TIA and minor ischemic stroke (POINT)

Study Protocol Training

Protocol Version 5.0_30Oct2013

Primary Objective

To determine whether clopidogrel 75 mg/day (after a loading dose of 600 mg) is effective in preventing major ischemic vascular events (ischemic stroke, myocardial infarction, and ischemic vascular death) at 90 days when subjects are randomized within 12 hours of time last known free of new ischemic symptoms in patients receiving aspirin 50-325 mg/day (with a dose of 150-200 mg daily for 5 days, followed by 75-100 mg daily for the remaining 85 days, strongly recommended).

Study Design

- Prospective, randomized, double-blind, multicenter trial, with approximately 350 participating sites and 5,840 subjects.
- Primary null hypothesis:
  - No difference in the event-free survival at 90 days in those treated with clopidogrel (600 mg loading dose then 75 mg/day) compared to placebo when subjects are randomized within 12 hours of time last known free of new ischemic symptoms.

Patient Population

Patients 18 years of age or older with high-risk TIA (defined as an $ABCD^2$ score ≥ 4) or minor ischemic stroke (with NIHSS ≤3) who can be randomized within 12 hours of time last known free of new ischemic symptoms.

Inclusion Criteria

- 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 $ABCD^2$ score ≥4 ***or***
  - **Minor ischemic stroke**: Residual deficit with NIHSS ≤3 at the time of randomization.
- Ability to randomize within 12 hours of time last known free of new ischemic symptoms.

Inclusion Criteria

- Head CT or MRI ruling out hemorrhage, or other pathology, such as vascular malformation, tumor, or abscess, that could explain symptoms or contraindicate therapy.

- Ability to tolerate aspirin at a dose of 50-325 mg/day.

Exclusion Criteria

- Age <18 years.
- TIA symptoms limited to isolated numbness, isolated visual changes, or isolated dizziness/vertigo.
- In the judgement of the treating physician, a candidate for thrombolysis, endarterectomy or endovascular intervention, unless the subject declines both endarterectomy and endovascular intervention at the time of evaluation for eligibility.
- Receipt of any intravenous or intra-arterial thrombolysis within 1 week prior to index event.
- Gastrointestinal bleed or major surgery within 3 months prior to index event.

Exclusion Criteria (continued)

- History of nontraumatic intracranial hemorrhage.
- Clear indication for anticoagulation (e.g., warfarin, heparin) anticipated during study period (atrial fibrillation, mechanical heart valve, deep venous thrombosis, pulmonary embolism, antiphospholipid antibody syndrome, hypercoagulable state).
- Qualifying ischemic event induced by angiography or surgery.
- Severe non-cardiovascular comorbidity with life expectancy <3 months.
- Not willing or able to discontinue prohibited concomitant medications
- Inability to swallow medications.

Exclusion Criteria (continued)

- Contraindication to clopidogrel or aspirin:
  - Known allergy
  - Severe renal (serum creatinine >2 mg/dL or 176.8umol/L) or hepatic insufficiency (prior or concurrent diagnosis, with INR>1.5, or any resultant complication, such as variceal bleeding, encephalopathy, or icterus)
  - Hemostatic disorder or systemic bleeding in the past 3 months
  - Current thrombocytopenia (platelet count <100 x 10^9/l) or neutropenia/granulocytopenia (1 x 10^9/l)
  - History of drug-induced hematologic or hepatic abnormalities

Exclusion Criteria (continued)

- Anticipated requirement for long-term (>7 day) non-study antiplatelet drugs (e.g. dipyridamole, clopidogrel, ticlopidine) or NSAIDs affecting platelet function (such as prior vascular stent or arthritis).
- 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).

Exclusion Criteria (continued)

- Unavailability for follow-up.
- Signed and dated informed consent not obtained from patient.
- Other neurological conditions that would complicate assessment of outcomes during follow-up.
- Ongoing treatment in another study of an investigation therapy, or treatment in such a study within the last 7 days.
- Previously enrolled in this study.

Optional Biomarkers Ancillary Study

- Participants who consent to the POINT Trial will be asked to consent to an optional ancillary study consisting of a one-time venous blood sample of approximately 10mL collected at the time of enrollment in the trial.
- Samples used for testing the specific hypothesis as to whether clopidogrel resistant genotypes modify the stroke prevention response in high-risk TIA patients.

Optional Biomarkers Ancillary Study

- **Primary Objective**
  - To examine the relative risk of vascular outcome events for carriers (of specific ABCB1 and CYP2C19 genotypes) versus non-carriers amongst those receiving clopidogrel.
- **Secondary Objective**
  - Subgroup analysis by the enrolling/index event type (either TIA or minor ischemic stroke cohort) performed separately for the TIA cohort and the minor ischemic stroke cohort.

Study Drug Handling

- **Supply and Storage**
  - The UCSF Drug Product Services Lab (DPSL) will distribute blinded investigational products (active drug and placebo).
  - Active drug/placebo stored at site in secure, safe place at room temperature (77^{o}F; range: 59^{o}F-86^{o}F).
  - Kept under responsibility of Investigator or other authorized individual.
- **Packaging**
  - 97 tablets of active drug or placebo (8 for load, 89 for subsequent daily use) supplied in pre-packaged bottles.

Study Drug Handling (continued)

- **Dispensing**
  - **Day 1 Loading Dose:**
    - Subject should take loading dose (8 tablets of study drug) and first dose of aspirin while study investigator or other member of study team is present.
    - The dose of aspirin during enrollment is 50-325mg daily, at discretion of treating physician; strongly recommended dose is 150-200mg daily for 5 days followed by 75-100mg daily for the remaining 85 days.
  - **Day 2 to 90**:
    - One (1) pill of study drug or placebo, as well as one (1) prescribed dose of 50-325mg aspirin daily.
- **Refer to "Pharmacy Study Drug Handling SOP" on the NETT website Toolbox: https://sitemaker.umich.edu/nett/point_toolbox**

Study Drug Handling (continued)

- PPIs are discouraged in patients enrolled in POINT.
  - If patient is felt to need medication for gastroesophageal reflux disease, preferred medications would be H2 blockers, such as famotidine 20mg twice daily, or ranitidine 150mg twice daily.

- If a patient is felt to require treatment with a PPI during enrollment, and is not felt to be a candidate for another medication such as an H2 blocker, the first choice of PPI agent would be **pantoprazole 40mg daily.**

Study Drug Ordering & Accountability

- **Ordering**
  - Once the UCSF Drug Product Services Laboratory (DPSL) receives notice that a site has been initiated, sends initial shipment of 6 bottles (3/3) via FedEx to site.
  - Resupply of active drug and placebo automated; when available study drug reduced to four (4) bottles at site, a recruitment-based algorithm used to calculate number needed for next 12 months, based on previous rate of recruitment.
- **Accountability**
  - Spoke/Site staff confirms receipt and completes Randomization Verification process for each bottle in WebDCU™ system.
- **Destruction**
  - Destroyed on site following local medical waste standards, site guidelines, and any local SOPs in place for disposition of unusable study drug.
  - Drug should not be destroyed on site until after the first monitoring visit has been completed.

Prohibited Concomitant Treatments

- NSAIDs, Cox1 inhibitors (NSAIDs given for as short a time as possible, not sooner than 8 days after randomization)
- Anticoagulants (both oral and parenteral)
- Open-label thienopyridines (e.g., ticlopidine, clopidogrel)
- Dipyridamole
- Other antiplatelets
- Thrombolytics (e.g., tPA)
- Vascular intervention (surgery and/or angioplasty of any vessel)

If there is a clinical need that justifies added risk of these interventions in setting of study drug use, they should be employed at discretion of treating physician.

Discontinuing Study Medication

- If intervention absolutely necessary during study period and treating physician deems it necessary, stop study drug for 5 days prior to intervention.
- Restart study treatment as soon as felt to be safe; subject followed until 90 days.

PERMANENT TREATMENT DISCONTINUATION

- A subject should discontinue study drug for any of the following reasons:
  - Intercurrent condition requiring discontinuation of study drug.
  - Positive serum pregnancy test, desire to become pregnant, or contraception cessation.
  - Clear indication for anticoagulation.

Emergency Unblinding Procedure

- Care of subjects should not require unblinding, but we are prepared to unblind if absolutely necessary.
- Medication bottles will be coded with unique randomization numbers.
- In case of emergency need for unblinding of a subject, the clinical site PI or his/her designee calls the UCSF CCC emergency phone number, **1-866-94-POINT (1-866-947-6468)** or **415-663-4444** for unblinding through the WebDCU™ system.
- See WebDCU™ Manual for additional information.

Randomization Emergency Hotline

- The WebDCU™Randomization Emergency Hotline (**1-866-450-2016**) has been established for emergency randomization issues.
- If you encounter problems trying to randomize in the WebDCU™ system of it there is a problem with the randomization assignment generated by the WebDCU™ system, call the 24-Hour WebDCU™Randomization Emergency Hotline: **1-866-450-2016.**

Serious Adverse Events

- **Only serious adverse events (SAEs)** collected for POINT.
- SAE = Any adverse event that is
  - fatal or life-threatening
  - permanently or substantially disabling
  - requires or prolongs hospitalization
  - results in a congenital anomaly or
  - requires intervention to prevent permanent impairment or damage.

U.S. sites MUST submit these SAEs to their IRB in accordance with local reporting requirements. For O.U.S. sites, the CRC Medical Monitor is notified when an event is determined to be a serious, unexpected, adverse reaction by the CEC. The CRC Medical Monitor completes the Council for International Organizations of Medical Sciences (CIOMS) form and sends it to the country-level Regulatory Manager for sites outside the US. The country level manager submits the form to the country level regulatory agency.

Outcome and SAE Reporting

- Outcome Events and SAEs may be discovered at any time during the subject's enrollment, including 7-day telephone follow up, 30-day contact or 90-day follow up contact or visit.
- When an Outcome Event or SAE is discovered, the site PI is responsible for recording it **within 5 days** of the event.
  - The online SAE/Clinical Outcome Form (CRF 19) should entered and **submitted** into WebDCU™ **within 5 days** of discovery.
  - Detailed description of event, relevant tests/laboratory data should be included in the narrative to assist in reviewing the event.
  - Include Event Packet Checklist, accessed through CRF 19.

Outcome and SAE Reporting (continued)

- WebDCU™ triggers an automatic email notification of the SAE/Outcome Event to the NETT or CRC Site Manager.
- Site PI works with the Site Manager to prepare an **event packet** (with all unique identifiers removed), including:
  - Basic packet:
    - Copies of discharge summaries (index and outcome events)
    - Head imaging reports (index and outcome events)
    - Neurology or cardiology consultation notes
  - Supplemental documentation based upon adjudication category assigned to the event (see outcome event-specific checklist for a complete list)
  - Documents requiring translation will be checked for deletion of PHI by the country level manager, and a request for translation will be made to the CRC. The CRC will provide the translated documents back to the country level manager for upload.
- When complete, the event packet is uploaded into WebDCU™, an automatic email notification is sent to the Clinician Event Coordinator (CEC) at UCSF who reviews the event, and indicates whether the event is serious, unexpected and study drug-related.

Outcome and SAE Reporting (continued)

- CEC indicates if event is neurological, cardiovascular, or systemic.
- Adjudication system assigns two reviewers to event based on type of event.
- If both reviewers agree, then final adjudication entered into database.
- If unable to agree, then third Adjudicator assigned to review.
- If third Adjudicator does not agree with one of the other two Adjudicators, the Adjudication Committee Chair facilitates agreement. The Adjudication Committee Chair's decision is the final determination.

Outcome and SAE Reporting (continued)

- Outcomes to be reported include:
  - Ischemic Stroke
  - TIA
  - Symptomatic Hemorrhagic Transformation of an Ischemic Stroke
  - Asymptomatic Hemorrhagic Transformation of an Ischemic Stroke
  - Symptomatic Intracerebral Hemorrhage
  - Asymptomatic Intracerebral Hemorrhage
  - Other Symptomatic Intracranial Hemorrhage
  - Other Asymptomatic Intracranial Hemorrhage
  - Myocardial Infarction with and without Coronary Revascularization
  - Coronary Revascularization without Myocardial Infarction
  - Major Hemorrhage other than Intracranial Hemorrhage (life threatening or non-life threatening)
  - Minor Hemorrhage other than Intracranial Hemorrhage

Baseline Evaluation

- Assess inclusion and exclusion criteria.
  - Administer scales: $ABCD^2$; NIH Stroke Scale (NIHSS)
  - Patient demographic information
  - Symptoms of the index event
  - Prior medications; past medical history; smoking history
  - Blood pressure
  - Laboratory evaluation (part of usual care)
    - Head imaging, laboratories (CBC, INR, glucose), ECG
    - Carotid artery imaging will be encouraged but not required
    - Record results for other diagnostic studies such as cervicocerebral MRA or CTA
    - Antiplatelet and anticoagulant agents other than aspirin will be discontinued prior to randomization
- If not eligible, complete Screen Failure Log.
- Written, signed and dated informed consent will be obtained prior to randomization and all other study procedures.

Schedule of Events

Measurements	Screening	Baseline/ Randomization	Phone F/U Day 7+/-2	Phone F/U Day 30◊	Phone or In-Person F/U Day 90+/-14†	Event Visit***	End of Study
Screen Failure Log	x						
Eligibility Form		x					
Consent (including optional study)		x					
Randomization Form		x					
Enrollment/ Demographics		x					
ABCD^2 Score		x					
Modified Rankin Scale					x	x	
NIH Stroke Scale		x			x	x	x
Medical History		x					
Prior Medications		x					
Index TIA/Minor Stroke Symptoms		x					
Vital Signs		x					
Blood Sample (optional)		x*2					
Head CT/MRI Scan		x*			x*	x*	
ECG		x*			x*	x*	
Carotid Imaging		x*1			x*1	x*	
Stroke-Free Questionnaire: QVSFS			x		x	x	
Morisky Questionnaire			x		x	x	

Schedule of Events (continued)

Measurements	Screening	Baseline/ Randomization	Phone F/U Day 7+/-2	Phone F/U Day 30Θ	Phone or In-Person F/U Day 90+/-14†	Event Visit***	End of Study
Concomitant Medications Form			x		x	x	
SAE/Clinical Outcome Reporting Form			x		x	x	
Study Drug Compliance							x
Final Diagnosis		x					
End of Study Form							x
Protocol Violation	x	x	x		x	x	x

* Part of standard evaluation; cost not covered by study.
** As needed (visit can occur more than once).
*** Event Visits for MI can be completed by telephone.
† Preferably as soon as possible after the completion of 90 days.
[1] Encouraged as part of best practices but not required for study entry or at 90 days. If performed, record results on CRF.
[2] Blood sample obtained with subject's consent for optional ancillary study.
Θ No study data collected.

Note: Certain follow-up assessments, such as modified Rankin and QVSFS, by telemedicine are acceptable.

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Randomization

- Determine patient's eligibility; obtain written, signed and dated informed consent.
- **Qualified** site personnel access Randomization Interface in WebDCU™ and complete a randomization form.
- If patient eligible based on the information provided, WebDCU will generate a randomization number, which corresponds to one of the medication bottles
- Randomization number appears on the screen, automatic confirmatory e-mail is sent and *Randomization Verification Form* (RVF) is printed and brought to pharmacy.
- Medication bottle with corresponding randomization number selected, verified (with completion of RVF) and loading dose is administered with a witness present.
- At discharge, the study medication bottle is given to the subject with appropriate instructions for daily administration.

7-day Follow-up Phone Call

- The Site Coordinator will contact subjects by telephone (or in person) at 7 days, +/- 2 days.
- Potential SAEs/Clinical Outcomes, concomitant medications and compliance with study medication using the Morisky Questionnaire will be assessed.
- The QVSFS will be administered and the Seven Day Follow Up form will be completed.
- An Event Visit will be scheduled whenever subject contact suggests that a possible stroke, TIA or MI may have occurred.

30-day Contact

- The Site Coordinator will contact subjects by telephone (or in person) at 30 days, +/- 2 days to uncover any issues or concerns that might impact study drug compliance and retention in the study. No data will be collected.
- An in-person or telephone Outcome Event Visit should be conducted whenever subject contact suggests that a possible stroke, TIA or MI may have occurred. Outcome Event Visits can be conducted via telephone if the subject experiences a myocardial infarction. Stroke and TIA events can be evaluated via telemedicine when necessary.

90-Day Follow-up

- In-person or telephone contact at 90 days, +/- 14 days, to review:
  - SAEs/Clinical Outcomes
  - Concomitant medications
  - Compliance with study medication (Morisky Questionnaire)
  - QVSFS, mRS, NIHSS results
- The study physician will:
  - Discuss options for antiplatelet therapy;
  - Confirm that a high-dose, high-potency statin is also prescribed, and that blood pressure and diabetes are well controlled; and
  - Discuss diet, exercise, and appropriate action in the event of stroke.

90-Day Follow-up (continued)

- The 90-day assessment does not have to be completed by the PI. It can be completed by anyone on the study team that has completed the appropriate POINT study training and whose certifications are current.

Outcome Event Visit

- Occurs whenever subject contact suggests that a possible stroke, TIA or MI may have occurred. Can be conducted via telephone if the subject experiences MI. Stroke and TIA events can be evaluated via telemedicine when necessary.
  - May occur on the same day as the 90-day visit
  - May occur more than once for the same subject
- Appropriate laboratory testing will be required for documentation of systemic hemorrhage or other systemic complications.
- Autopsy will be encouraged when cause of death is unclear.
- If study medications are discontinued due to an outcome or SAE, they should be restarted as soon as felt to be safe by the treating physician.

Compliance and Retention

- Success of study depends on subject retention and compliance, and on minimizing lost to follow-up, dropouts and missed visits
- If subject consents to provide alternate contacts, obtain information for alternate contacts who could help locate the participant
- Establish and keep lines of communication open among PI, Study Coordinator and the participant
- Let NETT-CCC or POINT CRC know if help contacting the participant is needed
- 100% follow-up can be achieved!
- For urgent questions related to enrollment or unblinding, call the POINT Hotline, **1-866-94-POINT** (1-866-947-6468) or 415-663-4444

Minimizing Missed Visits

- EVEN if participant is no longer taking study medication, continue following *per protocol*
- If participant refuses further treatment, let participant know we want to continue the study visits and learn how they are doing - THIS IS VERY IMPORTANT
- To do otherwise may introduce bias and decrease the validity of our findings
- Remember - Once Randomized, Always Analyzed!
- Only participants who die or refuse to be followed for the study should have missed visits or missing data

Regulatory Binder

- POINT regulatory documents are managed in NETT Regulatory Document Database, a central regulatory document management system containing the interfaces and tables for managing the required electronic documents
  - Module eliminates duplicate effort by using centralized system
  - Section 10.0 of the POINT Procedures Manual contains full list of required regulatory documents
- Regulatory materials not uploaded to the module may include manual temperature log (if converted to PDF, logs can also be uploaded to module) and study correspondence outside of electronic communications.

Study Monitoring

- A Site Monitor will visit at least one during the study, after a site's first two subjects have completed the 90 day follow-up visit.
- A Site Monitor will also visit a site for cause, as needed.
- A Site Monitor may call from time to time to check in on a site's progress and offer any needed assistance.

Study Monitoring (continued)

- Sites may be monitored for cause, due to:
  - A request from the POINT Trial Executive Committee
  - The outcome of previous visit
  - A high or low accrual rate
  - Number of data corrections required
  - History of protocol deviations or non-compliance with GCPs
  - Staffing issues
  - DSMB or IRB request

Important Study Information

- POINT Hotline **1-866-94-POINT (1-866-947-6468)** or **415-663-4444** for urgent questions related to enrollment and/or unblinding.
- 24-Hour WebDCU Randomization Emergency Hotline **1-866-450-2016** for problems trying to randomize in WebDCU™ or problems with the randomization assignment generated by WebDCU™
- POINT websites
  - https://www.nett.umich.edu/nett/point_resources_and_training
- NETT CCC sites
  - Email POINT-trial@umich.edu
  - Phone 734-232-2142
- POINT CRC sites
  - Email CRC@emmes.com
  - Phone 1-800-305-7811

Protocol Training Assessment

- Complete the brief quiz at https://lessons.ummu.umich.edu/2k/point/point_training_assessment_01 to document completion of the POINT protocol training.

- Be sure to print the POINT Protocol Training Certificate upon completion of training module.