15.0 CONTROL OF STUDY DRUG

In compliance with 21 CFR §312.60, investigators in the POINT Trial are responsible for:

- ensuring that the investigation is conducted according to the signed statement, the investigational plan, and applicable regulations
- protecting the rights, safety, and welfare of study participants
- controlling drugs under investigation

Adequate control and handling of investigational drug includes all of the following:

- The investigator should ensure that the investigational drug is used only in accordance with the IRB/IEC/CHR-approved protocol.
- An investigator must administer the investigational drug only to participants under the investigator's direct personal supervision or under the supervision of a sub-investigator directly.
- The investigator must not supply the investigational drug to any person not authorized to receive it.
- An investigator is required to maintain adequate records of the disposition of the investigational drug, including dates of dispensing, quantity currently maintained for dispensing, and amount of the investigational product dispensed to participants.
- If the investigation is terminated, suspended, discontinued or completed, the investigator must return any unused supplies of the investigational drug to the study pharmacy, or otherwise provide for disposition of the unused supplies as directed by the UCSF CCC, study pharmacy and/or sponsor.

POINT investigators are required to adhere to the following regulations for documentation of the investigational drug:

- Prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. [21 CFR §312.62]
- Maintain case histories, including the case report forms and supporting data (e.g., signed and dated consent forms and medical records including progress notes of the physician, the individual's hospital chart(s), and the nurses' notes). The case history for each individual will document that informed consent was obtained prior to participation in the study.
15. 1 Study Investigational Pharmacy

The UCSF Drug Product Services Laboratory (DPSL) will function as the Central Pharmacy for the study for U.S. and international sites, in partnership with Sharp Clinical Services. The DPSL is the retail compounding pharmacy of the School of Pharmacy, Department of Clinical Pharmacy at the University of California, San Francisco.

Sharp Clinical Services will produce labels, with computer generated randomization codes, that are to be used for the bottle. Labels will be supplied to the DPSL by Sharp, and applied to the bottles of study drug.

15.2 Study Medication Handling

15.2.1 Study Medications

This randomized double-blind study is primarily designed to compare a clopidogrel/aspirin combination versus an aspirin alone regimen. The two types of study tablets (75 mg active clopidogrel and placebo) are indistinguishable, identical in size, shape, color, appearance, and taste. The tablets are pink, round, slightly biconvex, not engraved, and film-coated.

Sanofi will manufacture and supply the study drug and the placebo in amounts adequate to accommodate a minimum of 5,840 study subjects, in a 1:1 ratio between clopidogrel and placebo.

15.2.2 Clopidogrel

The clopidogrel used in the study will be supplied by Sanofi and distributed by the UCSF Drug Products Services Laboratory (DPSL) or in partnership with Sharp Clinical Services. It will be supplied in 75mg tablets.

The group assigned to clopidogrel will receive:

- Day 1: 8 tablets of clopidogrel 75mg (loading dose of 600mg) in addition to open label aspirin 50-325mg at the discretion of the treating physician
- Day 2-Day 90: one tablet of clopidogrel 75mg and 50-325mg of aspirin daily. Minor side effects are unusual with the medication, so it is not anticipated that either subjects or clinicians will be able to differentiate the placebo from the active drug. Standard laboratory tests cannot detect the effects of clopidogrel.

15.2.3 Placebo
The placebo used in the study will be supplied by Sanofi and distributed by the UCSF Drug Products Services Laboratory (DPSL) or in partnership with Sharp Clinical Services. The placebo is indistinguishable from clopidogrel tablets: identical in size, shape, color, appearance and taste.

The group assigned to placebo will receive:

- Day 1: 8 tablets of placebo (loading dose of 600mg) in addition to open label aspirin 50-325mg at the discretion of the treating physician.
- Day 2-90: one tablet of placebo and 50-325mg of aspirin daily. An aspirin dosing schedule of 150-200 mg daily for 5 days followed by 75-100 mg daily is recommended.

15.2.4 Aspirin

Aspirin tablets will be open label with the dose in a range of 50-325mg daily determined by the treating physician.

An aspirin dosing schedule of 150-200 mg daily for 5 days followed by 75-100 mg daily is recommended.

15.3 Concurrent Treatments

15.3.1 Prohibited concurrent treatments

Use of the following medications after randomization and during the study period represents a protocol violation. However, if there is a clinical need that justifies the added risk of these interventions in the setting of study drug use, they should be employed at the discretion of the treating physician.

- NSAIDs, Cox1 inhibitors: If absolutely necessary, NSAIDs may be given for as short a time as possible but not sooner than 8 days after randomization
- Open-label thienopyridines (ticlopidine, clopidogrel)
- Dipyridamole
- All heparins
- Oral anticoagulants (e.g., warfarin)
- Thrombolytics (e.g., tPA)
- Vascular intervention (surgery and/or angioplasty of any vessel).

If intervention is absolutely necessary within the three months after
randomization, study drug will be stopped 5 days prior to the intervention. Study treatment will then be restarted unless the patient needs to take open label clopidogrel or aspirin. In this case, study drug will be restarted only when treatment with open label antiplatelet therapy other than aspirin has been stopped.

15.3.2 Proton Pump Inhibitors

Clopidogrel is a prodrug (a substance administered in an inactive form that is then metabolized in the body in vivo into the active compound) that must be converted to its active form by liver cytochrome P-450 enzymes, particularly CYP2C19. In March 2010, a black box warning was added to the label for clopidogrel: “Reduced effectiveness in patients who are poor metabolizers of the drug – that some patients do not convert Plavix to its active form as well as other patients. These patients may not get the same benefit from Plavix and are known as poor metabolizers.”

Some writers have advocated genotyping patients prior to initiating clopidogrel therapy to determine if they carry a reduced-function gene variant (primarily the CYP2C19*2 polymorphism) because these carriers appear to have an excess risk of cardiovascular events and mortality on clopidogrel. Studies do not address cerebrovascular disease. This issue remains controversial and caused the American College of Cardiology Foundation/American Heart Association on June 28, 2010 to issue a Clopidogrel Clinical Alert: Approaches to the FDA “Boxed Warning” stating, “Overall, however, the evidence is insufficient to recommend routine genetic or platelet-function testing at the present.” [183] Also, in an important study regarding this matter, it was concluded that CYP2C19 loss-of-function variants do not modify the efficacy and safety of clopidogrel [184].

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

Proton-pump inhibitors (PPIs) also are metabolized by CYP2C19 and when taken concomitantly with clopidogrel can decrease the antiplatelet effectiveness of clopidogrel. One of the PPIs, pantoprazole, can be metabolized by enzymes other
than CYP2C19. For these reasons, POINT recommends that H2 antagonists be used when possible in subjects requiring gastroesophageal protection and for those not controlled with H2 antagonists and deemed to require a PPI, pantoprazole may be the best choice.

See Appendix XVI for a listing of prohibited medications.

15.3.2 Permitted concurrent medications

Any drugs other than those listed above are permitted at the discretion of the Investigator.

Any medication which is taken within the course of the study will be documented on the Concomitant Medication CRF.

15.4 Receipt of Study Drug

The DPSL and/or Sharp Clinical Services will receive, inspect and store the bottles of study drug provided by Sanofi. The bottles will be stored until they are packaged and shipped, expire or are no longer needed.

An inventory record of study drug on hand will be maintained by the DPSL and/or Sharp Clinical Services.

15.5 Packaging

Each patient will be assigned 97 tablets of study drug (8 for loading dose, and 89 for subsequent daily use) according to the randomization assignment, to be used as directed.

15.6 Study Drugs

15.6.1 Baseline Visit

The subject should take the first eight pills of the study drug (loading dose) and the first dose of aspirin while the POINT study investigator or study coordinator is present. The dose of aspirin (50-325mg) should be determined by the treating physician, but a dose of 150-200 mg daily for 5 days followed by 75-100 mg daily is strongly recommended.

The subject should continue to take the study drug and aspirin throughout the study period. Each subject should take one pill of study drug or placebo, as well as one prescribed dose of 50-325mg aspirin daily.

15.6.2 Follow up Visits
Each participant will have a telephone evaluation with their site coordinator on day 7 (+/- 2 days) and on day 30 after randomization. The Morisky Questionnaire for assessing compliance with the study medication regimen will be administered during this telephone call. The final study visit at 90 days will also include administration of the Morisky Questionnaire and a pill count to determine medication regimen compliance.

15.6.3 Dispensing Schedule

Subjects in the study will be given a single bottle containing 97 tablets of either active drug or placebo. Subjects will be encouraged to complete a log documenting their compliance with the study medication regimen.

15.7 Pharmacy

15.7.1 Control: Shipping, Packing, Storing

Sanofi will ship active drug and placebo direct to the UCSF DPSL and/or Sharp Clinical Services. The drug will be supplied in sealed bottles containing 97 tablets; no repackaging will be necessary. The drug can be stored at room temperature, with permitted excursions. The DPSL and/or Sharp Clinical Services will receive an automatic email notification when a site has been initiated and is ready to receive study drug.

15.7.2 Dispensing

Drug will be shipped to and distributed to each participating site following its own approved local procedures. The study allows drug to be shipped to and distributed from a pharmacy or from the clinical offices of the participating site. Sites will track receipt, usage, and disposal of study medications in WebDCU™. Participating sites should use their own approved local procedures for disposal of any unused study medication.

15.7.3 Drug Accountability

See the WebDCU™ Manual for more information.