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

Changes to Protocol version 6.0 from version 5.0

- **Throughout the document:** Various spacing, format, layout changes
- **Title Page**: Changed Version # and date
- **Title Page**: Add Anthony Kim, MD, MAS as Co-Principal Investigator with related credentials
- **Footer**: Changed Version # and date
- **Table of Contents**: Adjusted page numbering
- **Page 10, POINT Protocol Synopsis, Exclusion Criteria**: Changed

  Ongoing treatment in another study of an investigational therapy, or treatment in such a study within the last 7 days.
  to
  Ongoing treatment in another study of an investigational therapy that may potentially interact with study drug, or treatment in such a study within the last 7 days.

- **Page 18, Section 2.4 Potential Therapies:** Added

  Usman et al. report metanalyses of 13 studies comparing mean bleeding frequencies for aspirin (≤325 mg/day), clopidogrel, anticoagulants (warfarin and other vitamin K antagonists), aspirin plus clopidogrel, and aspirin plus extended-release dipyridamole (ER-DP). Total bleeding occurred at mean rates of 4.8% with aspirin (≤325 mg/day) alone, 2.9% with clopidogrel alone, 3.6% with aspirin plus ER-DP, 10.1% with aspirin plus clopidogrel, and 16.8% with anticoagulation. Major bleeding occurred at mean rates of 1% with aspirin (≤325 mg/day) alone, 0.85% with clopidogrel, 0.93% with aspirin plus ER-DP, 1.7% with aspirin plus clopidogrel, and 2.5% with anticoagulation. In conclusion, the combination of aspirin and clopidogrel is associated with significantly greater bleeding than either aspirin (≤325 mg/day) or clopidogrel alone. Aspirin plus ER-DP has a greater bleeding rate than clopidogrel but a lower rate than aspirin (≤325 mg/day) alone. [186]

- **Page 26, Section 4.3 Organizational Structure and Communication Flow**: Removed duplicate entry
- **Page 29, Section 4.3.1 Trial Organization**: Changed

  Sanofi has agreed to contribute clopidogrel and its placebo at no cost and with no restrictions.
  to
  Sanofi has agreed to supplied clopidogrel and its placebo at no cost and with no restrictions through May 2016, when its contract for POINT will end. From May 2016 forward, additional supplies of study drug will be provided by Sharp Clinical Services, Inc.

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- **Page 35, Section 5.2 Inclusion and Exclusion Criteria:** Changed

  Ongoing treatment in another study of an investigational therapy, or treatment in such a study within the last 7 days.

  to

  Ongoing treatment in another study of an investigational therapy that may potentially interact with study drug, or treatment in such a study within the last 7 days.

- **Page 35**, **Section 6.1 Study Drug**: Changed

  Sanofi will supply the following blinded study drugs, which will be distributed by the UCSF Drug Product Service Laboratory (DPSL) for US sites and Pharmacy Services partners for OUS sites:

  - *Clopidogrel 75mg tablets*
  - *Placebo tablets*

  to

  Sanofi supplied the blinded study drugs, clopidogrel 75mg and matching placebo, distributed by the UCSF Drug Product Service Laboratory (DPSL) for US sites and Pharmacy Services partners for OUS sites in quantities sufficient to last through May 2016, when its contract for POINT will end. From May 2016 forward, additional supplies of blinded study drug (clopidogrel and matched placebo) will be provided by Sharp Clinical Services, Inc. in quantities sufficient to last through the end of enrollment.

- **Page 36, Section 7.1 Supply and Storage**: Changed

  The manufacturer Sanofi will supply the blinded study drugs (clopidogrel 75mg tablets, and placebo to match clopidogrel tablets) used in the study in bottles containing 97 tablets (eight (8) tablets for loading dose, and a 89-day supply for one tablet daily). The study drug will be distributed by the UCSF Drug Product Services Laboratory (DPSL) to sites in the United States, and by Pharmacy Services partners to sites outside the US.
  There will be at least three drug shipments for the study: Sanofi will initially ship clopidogrel and placebo to the UCSF DPSL in April 2010 with a second shipment in 2012 and a third shipment will be sent in the second quarter of 2014.

  to

  The manufacturer Sanofi supplied the blinded study drugs (clopidogrel 75mg tablets, and placebo to match clopidogrel tablets) used in POINT and distributed by the UCSF Drug Product Services Laboratory (DPSL) to sites in the United States, and by Pharmacy Services partners to sites outside the US in quantities sufficient through May 2016. The contract with Sanofi will

end in May 2016; additional supplies of study drug after that date will be provided by Sharp Clinical Services, Inc. in quantities sufficient to last through the end of enrollment.

There will be at least four drug shipments for the study: Sanofi will ship clopidogrel and placebo to the UCSF DPSL in April 2010 with a second shipment in 2012 and a third shipment will be sent in the second quarter of 2014. The fourth shipment will be handled by Sharp Clinical Services in May 2016. A fifth shipment may be necessary, and will depend on the expiration dates and the rate of enrollment into the study. After May 2016, supplies …

- **Page 37, Section 7.1 Supply and Storage**: Changed *the DPSL* **to** *Sharp Clinical Services*

- **Page 37, Section 7.1 Supply and Storage**: Changed

  Storage temperature should be monitored at least daily and preferably by a continuous automated measuring and recording device. A manual temperature log must be maintained if automated temperature surveillance is not possible.
  to
  Storage temperature should be monitored and recorded daily, preferably by a continuous automated measuring and recording device. A daily manual temperature log must be maintained if automated temperature surveillance is not possible.

- **Page 37, Section 7.1 Supply and Storage**: Changed

  Contact the UCSF-CCC and, if necessary, Sanofi
  to
  Contact the UCSF-CCC and, if necessary, Sanofi (through May 2016) and Sharp Clinical Services thereafter

- **Page 37, Section 7.2 Packaging**: Changed *…labels…* **to** *…labels for shipments one to three…*

- **Page 38, Section 7.2 Packaging**: Changed

  The labels will be shipped to UCSF DPSL and to the Pharmacy Services partners, which will be responsible for labeling the bottles.
  to
  The labels for shipments four and five will be produced by Sharp Clinical Services and affixed to the bottles of study drug by Sharp as well.

Page 42, Section 8.5.1 SAEs/Clinical Outcomes into the Study Database: Changed *8.5.2* **to** *8.5.1.*

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Page 42, Section 8.5.1 SAEs/Clinical Outcomes into the Study Database: Changed … *within 5 days* **to** … *within 5 days (24 hours for sites in the UK)*

Page 43, Section 8.5.3 Procedure for Expedited Reporting of SAEs/Clinical Outcomes: Changed … *within 5 days* **to** … *within 5 days (24 hours for sites in the UK)*

- **Page 47, Section 9.1: Procedure for Expedited Reporting of SAEs/Clinical Outcomes**: Changed

  … *a properly trained and certified non-physician investigator* **to** … *properly trained and certified study personnel*

- **Page 52, 9.4.2 90 Day In-Person or Phone Follow-Up:** Added *For visits completed over the phone, the omission of the NIHSS assessment will not result in a protocol deviation.*

- **Page 53, 9.4.2.1 Subjects Considered Lost To Follow-up:** Changed *POINT Clinical Sites will need to demonstrate …* **to** *POINT Clinical Sites will need to demonstrate and document in WebDCU (Form 17 – End of Study: General Comments field)…*

- **Page 53, 9.4.2.1 Subjects Considered Lost To Follow-up:** Added *When subjects cannot be contacted despite the site team implementing these approaches, investigators should attempt to determine the subject's vital status at 90 days (i.e., living or deceased) using locally-approved resources.*

- **Page 68, Section 15 References**: Updated links in *references 149 and 150*.

- **Page 70, References**: Added *reference 186.*