point–ers

The Newsletter of the POINT Trial

Volume 6, Issue 1 1st/2nd Quarter 2016

2016 1st/2nd Quarter Recap

Dear Colleagues,

We apologize for the delay in getting the newsletter out. There is much to report about the first half of 2016.

Study Drug Restocking
We completed the replacement of study drug expiring August 31st at US sites on June 3, 2016. Domestic sites that have approval for amendment 6 of the protocol have resumed enrollment. We expect OUS sites (Outside of the United States) will be able to resume enrolling in late July or early August. For more information on international drug restocking, please see page 2.

May DSMB and Interim Analysis
Topics for the May 2, 2016 DSMB meeting included new study drug, funding, and the preliminary results of the SOCRATES trial. This meeting also marked our second interim analysis. The DSMB continues to believe that "POINT is a medically significant trial" and that it should "continue per its current protocol."

Initial SOCRATES Results
In March, AstraZeneca, the sponsor of SOCRATES, reported that ticagrelor was not found to be superior to aspirin in reducing the rate of stroke, myocardial infarction or death at 90 days. These results mean that the rationale for continuing POINT is greater than ever. For more information on the results of SOCRATES and what this means for our trial, see the article on page 2.

Study Enrollment Update
In both January and May we enrolled 86 participants, tying for our highest enrolling month ever! We currently have 3727 subjects in the trial, which is 63.8% toward our goal of 5840. Unfortunately, the delay in restocking study drug affected our enrollment rate in June, when we enrolled only 42 subjects. We need to get our international sites back up and running so we can meet our ongoing enrollment targets.

We continue to focus on bringing new sites on board, and plan to activate 28 international sites by the middle of 2017. So far this year we have activated sites in the United Kingdom, Germany, France, Spain, and Mexico. We are thrilled to welcome all new sites to the trial!

As always, please don't hesitate to contact us directly if you have questions or require more information.

Sincerely,

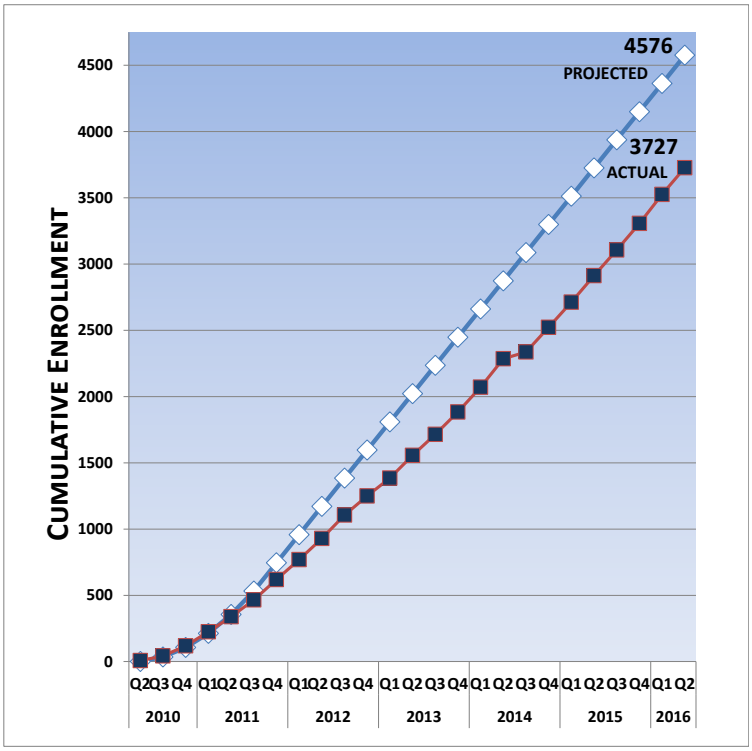
Clay Johnston MD, PhD, POINT Principal Investigator

Don Easton MD, POINT co-Principal Investigator

Anthony Kim MD, MAS, POINT co-Principal Investigator

POINT Cumulative Enrollment

May 2010 through June 2016



POINT Enrollment Update: Total = 3727

Hot Enrollers for 2nd Quarter

Place	Subjects	Site (Hub)
1	8	Stanford University (NETT),
2	7	Vall d'Hebron Hospital (CRC)
3	6	Benefis Hospitals (CRC), UCSF Medical Center (NETT), University of Calgary (CRC)
4	5	University of Alberta Hospital (CRC), Foch Hospital (CRC)

Top Enrollers (as of June 30, 2016)

Site (Hub)	City	State	#
Guilford Neurologic (CRC)	Greensboro	NC	110
Hospital of UPenn (UPenn)	Philadelphia	PA	106
Benefis Hospitals (CRC)	Great Falls	MT	81
Stanford Univ. (Stanford)	Stanford	CA	71
Buffalo General Med Ctr. (CRC)	Buffalo	NY	58
Columbia Univ. (NYP)	New York	NY	58
OHSU-Oregon (OHSU)	Portland	OR	57
Univ. of Alberta Hospital (CRC)	Edmonton	AB	57
Temple Univ. Hospital (Temple)	Philadelphia	PA	55
Detroit Receiving (Wayne)	Detroit	MI	54
Grady Memorial Hospital	Atlanta	GA	54
Houston Methodist(Texas)	Houston	TX	52
Univ. of Kentucky (Kentucky)	Kentucky	KY	49
Cleveland Clinic	Cleveland	OH	49

What do the SOCRATES Results Mean For POINT?

By Don Easton, MD, POINT co-Principal Investigator

The results of the SOCRATES trial were a disappointment, and a winner!

The result of the primary analysis was a "near miss." During the 90 days of treatment, a primary end-point event occurred in 6.7% of patients treated with ticagrelor versus 7.5% treated with aspirin (HR, 0.89; 95% CI, 0.78 to 1.01; P = 0.07). So, ticagrelor was not found to be superior to aspirin in reducing the rate of stroke, myocardial infarction, or death at 90 days.

At the same time, ischemic stroke occurred in 5.8% treated with ticagrelor and in 6.7% treated with aspirin (HR, 0.87; 95% CI, 0.76 to 1.00). This 0.9% reduction in the absolute stroke rate may seem small, but 74% of the strokes were fatal or disabling. Major bleeding occurred in 0.5% of patients treated with ticagrelor and in 0.6% of patients treated with aspirin, intracranial hemorrhage in 0.2% and 0.3%, respectively, and fatal bleeding in 0.1% and 0.1%. Additional interesting data will come in ongoing exploratory subset analyses.

These findings of possible efficacy for ticagrelor in prevention of stroke, without more bleeding than with aspirin, raise the possibility that ticagrelor plus aspirin could be more efficacious, at an acceptable risk for bleeding, than aspirin alone. A trial testing this hypothesis seems warranted.

What do the SOCRATES results mean for POINT?

The FDA almost certainly will not approve a stroke-prevention indication for ticagrelor, guidelines almost certainly will not recommend ticagrelor for stroke prevention, and therefore payers almost certainly will not reimburse for ticagrelor's use. Whether clopidogrel plus aspirin is more effective than aspirin alone, and acceptably safe, remains the key issue regarding antiplatelet treatment for prevention of atherothrombotic outcomes in patients with acute TIA and minor ischemic stroke.

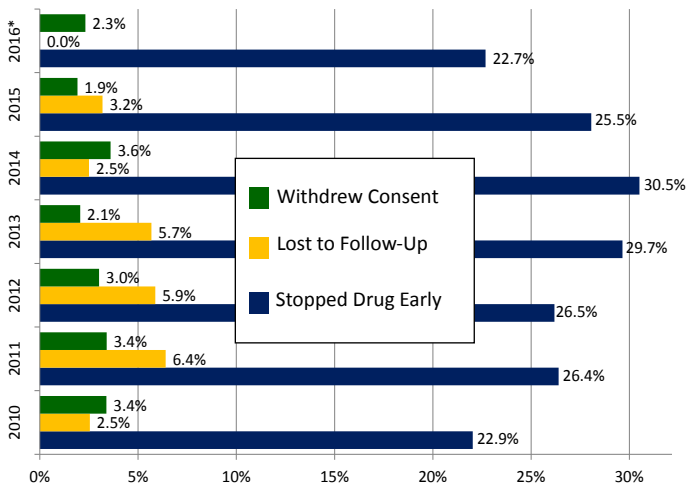
International Enrollment Delay

By Elizabeth Herbert, International Coordinator, CRC

Amendment 6 approvals remain pending for OUS sites. POINT has had a boost in enrollment since the inclusion of international sites, especially in the last quarter, with several sites in Spain, France, and Germany becoming active. However, the inclusion of OUS sites came with additional considerations of the regulations and the resulting different requirements for submission and approval. Each country required different additional documentation from the manufacturer in order to submit Amendment 6 for approval. Many of these documents were not available until the manufacturing process was complete. For US sites not requiring additional documentation from the manufacturer, submissions to IRBs were done in parallel with the manufacturing. This was not possible for OUS sites, and as a result, OUS sites are unable to enroll until approval from their respective country Competent Authority and/or Ethics Committee has been received. While OUS sites await approval of Amendment 6, US sites continue to contribute to our enrollment goals. We expect OUS countries to resume enrollment beginning in early July and continue through August.

If you have any questions about the enrollment delay, please send them to **PointOperations@ucsf.edu.**

Withdrawn Consents, Losses to Follow-Up, and Stopped Drug Early



Percent of Completed Subjects**

*May include subjects that have reached 90 days, but have no end of study form.
**Includes those reaching 90 days or completing the end of study form.
Data as of June 28, 2016

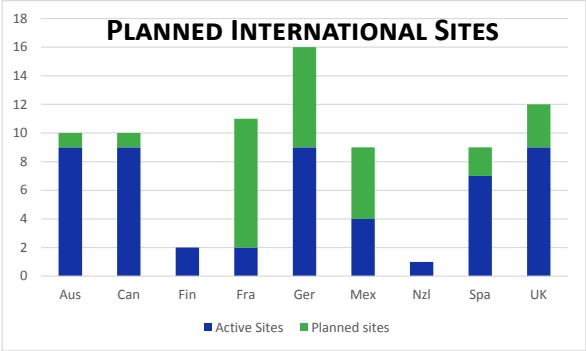
Top-Enrolling NETT Hubs (as of June 30, 2016)

Hub	Total	Enrollments per 90 days
UPenn	276	11.5
Cincinnati	169	6.9
Wayne	162	6.9
Minnesota	151	6.2

Q1 and Q2 Site Activations

University Hospital Heidelberg, Heidelberg, DEU (CRC); Neurological Clinic Bad Neustadt, Bad Neustadt/Saale, DEU (CRC); Central Bremen Hospital, Bremen, DEU (CRC); University Hospital Munster, Munster, DEU (CRC); **University Medical Center Hamburg, Hamburg, DEU (CRC)**; **Hannover Medical School, Hannover, DEU (CRC)**; Addenbrooke's Hospital, Cambridge, GBR (CRC); Culiacan General Hospital, Culiacan, SI, MEX (CRC), Vivantes Hospital Neukolln, Berlin, DUE (CRC); Basurto Hospital, Bilbao, ESP (CRC); Pierre Wertheimer Hospital, Bron, FRA (CRC); UC Davis Medical Center, CA (NETT); Bon Secours St. Mary's Hospital, VA (CRC)

***Bold text indicates sites that have already enrolled subjects.**



OUS Enrollment by Country (as of June 30, 2016)

Country	# Active Sites	Total Subjects
AUS/NZL	10	52
CAN	9	134
FIN	2	11
FRA	2	16
GER	9	3
MEX	4	6
SPA	7	107
UK	9	47