



StATins Use in intRacerebral hemorrhage patieNts

PROTOCOL TRAINING

Study Team

- Magdy Selim, MD, PhD (overall PI)
- Sharon Yeatts, PhD (Statistical PI)
- Pooja Khatri, MD (NCC PI)
- Ashkan Shoamanesh, MD, FRCP (Canadian PI)
- Jonathan Rosand, MD, MSc (Genetics Core PI)
- Barney Stern, MD (Independent Medical Safety Monitor)
- Steven Greenberg, MD, PhD (Adjudication Committee)
- Enrique Leira, MD, MS (Adjudication Committee)
- David Tirschwell, MD, MSc (Adjudication Committee)
- Daniel Woo, MD, MS (Adjudication Committee)
- Valerie Durkalski, PhD (unblinded Statistician)
- Rustam Al Shahi Salman, MA, MB BChir, PhD, FRCP (Adviser)

Study Team

- **Kimberlee Bernstein, BS, CCRP (NCC Project Manager)**
- **Sarah Marchina, PhD (BIDMC Project Manager)**
- **Katie Stever (WebDCU Data Manager)**
- **Aaron Perlmutter (NDMC Site Monitoring Manager)**

NIH/NINDS

- **Clinton Wright, MD, MS, Director, Division of Clinical Research**
- **Claudia Moy, PhD, Scientific Program Director**
- **Scott Janis, PhD, Administrative Program Director**
- **Joanna Vivalda, Administrative Project Manager**
- **Peter Gilbert, MS, Liaison NINDS DSMB**

Study Background and Rationale



Study Background and Rationale

- There is clinical equipoise as to whether statins should be continued or discontinued in patients with lobar intracerebral hemorrhage, who have a high risk for ICH recurrence and about the clinical circumstances under which statin drugs should be avoided
- Observational studies suggest that the risk of intracerebral hemorrhage decreases with increasing cholesterol levels and that low LDL-cholesterol level may be associated with increased risk for hemorrhagic stroke
- Furthermore, statin use is independently associated with the presence and number of cerebral microbleeds, including those in cortical locations, and confers a higher risk for lobar hemorrhage in patients carrying APOE $\epsilon 2$ and $\epsilon 4$ genotypes
- Statin drugs might increase the propensity for intracerebral hemorrhage by inhibiting platelets, decreasing thrombus formation, and enhancing fibrinolysis

Study Background and Rationale

- On the contrary, there is evidence that statins have pleotropic effects and could enhance recovery after stroke, and that discontinuation of statins is associated with worse outcomes
- The number of elderly patients taking statins is rapidly growing and is expected to rise further in the coming years. There is no consensus regarding the use of statin drugs in patients with lobar intracerebral hemorrhage, and strong evidence to support decision-making is lacking
- There are no prospective or randomized data on the effects of continuation vs. discontinuation of statin drugs after intracerebral hemorrhage on the risk of hemorrhage recurrence, incidence of major adverse cardiovascular events and ischemic stroke, and long-term functional and cognitive outcomes
- The goal of SATURN is to determine whether continuation vs. discontinuation of statin drugs is the best strategy in patients with lobar intracerebral hemorrhage with possible cerebral amyloid angiopathy, who are at high risk for recurrent intracerebral hemorrhage



SATURN

The **FIRST** and **LARGEST** **NINDS-funded ICH** **Prevention Trial**

Why Secondary Prevention for ICH?

- ICH is a frequent cause of long-term permanent disability & mortality
- BUT, did you know that.....
 - Recovery after ICH tends to be slower but often greater compared with ischemic stroke
 - Up to one-third of ICH survivors achieve mRS <2 by 90 days and even more by 6 months

A large number of ICH survivors are independent and would benefit from prevention of ICH recurrence

Study Objectives



Primary Objectives

- To evaluate the effects of continuation vs. discontinuation of statins on the risk of symptomatic intracerebral hemorrhage recurrence during 24 months of follow-up in patients presenting with a spontaneous lobar intracerebral hemorrhage while taking a statin drug
- To determine the effects of discontinuation vs. continuation of statins on the occurrence of any of the following major adverse cardio- and cerebrovascular events:
 - Symptomatic ischemic stroke
 - Symptomatic myocardial infarction
 - Newly symptomatic arterial occlusive disease (peripheral, retinal, or carotid)
 - Revascularization procedures for coronary, carotid, or peripheral arterial disease
 - Vascular death



Secondary Objectives

- To examine quality of life, functional, and cognitive outcomes in patients in whom statins are continued vs. discontinued, by repeated assessments of the EQ-5D quality of life questionnaire, modified Rankin Scale (mRS), and Telephone Montreal Cognitive Assessment (T-MoCA) at 3, 6, 9, 12, 18, and 24 months.
- To prospectively examine whether the presence vs. absence of APOE ϵ 4 and APOE ϵ 2 genotypes modifies the effects of statins on the risk of recurrent ICH, i.e., whether APOE genotype can be used as a biological marker to stratify the risk of ICH recurrence in statins-treated patients
- To determine whether the effects of continuation/discontinuation of statins on the risk of ICH recurrence and major adverse cardio- and cerebrovascular events vary by sex or ethnicity.

Exploratory Objectives

- To determine whether the risk of ICH recurrence on statin therapy is dose- (intensive vs. non-intensive) or agent- (lipophilic vs. hydrophilic) dependent
- To examine the impact of post-randomization variability in the use of anti-thrombotic agents, adequacy of blood pressure control, and use of other concomitant medications such as ACE inhibitors & beta-blockers on outcomes

Study Design and Procedures



Study Design

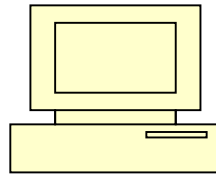
- Pragmatic, prospective, randomized, open-label, and blinded end-point assessment (PROBE) clinical trial
- 1456 subjects - 140 sites (US and Canada)
- Patients with spontaneous lobar ICH while taking statins will be randomized within 7 days of ICH to one of two treatment strategies: continuation vs. discontinuation of statin therapy (same drug; same dose)
- Randomization ratio = 1:1
- All subjects will be followed for 24 months, and will undergo baseline testing for APOE genotype
- Participants will undergo repeated structured assessments by phone during the follow-up period

Study Assessments Flowchart



Screening

- ✓ Inclusion
- ✓ Exclusion



Randomization

- ✓ ICH score
- ✓ NIHSS

APOE



Discharge

- ✓ mRS
- ✓ NIHSS



1, 2, 3, 6, 9, 12, 18, 24 months*

- ✓ Recurrent symptomatic ICH; MACE; SAEs; mRS; TMoCA; QoL (EQ-5D); Review of prescription refills; BP reporting

****All follow-up assessments will be performed by centralized evaluators. A central adjudication committee blinded to treatment allocation will adjudicate all outcome events and imaging data.***

Each subject will be followed for 24 months, including those who experience a recurrent ICH, to standardize the timing of final assessments of quality of life and functional/cognitive outcomes among all participants.

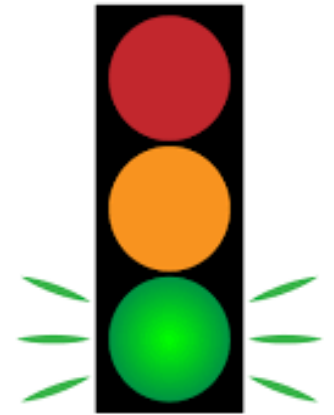
****MACE = Major adverse cardio- and cerebrovascular events**

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Inclusion Criteria

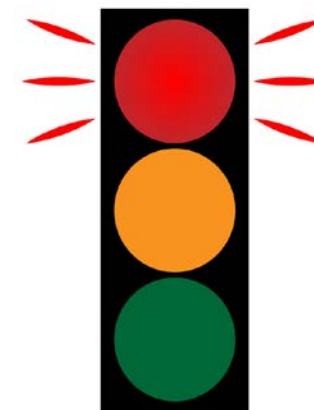
1. Age ≥ 50 years
2. Spontaneous lobar ICH*, confirmed by CT or MRI scan
3. Patient was taking a statin drug prior to the onset of the qualifying/index ICH
4. Randomization to one of the two treatment strategies can be carried out within 7 days of the onset of the qualifying ICH
5. Patient or surrogate after consultation with his/her physicians, agrees to be randomized to statin continuation vs. discontinuation and to provide written informed consent.

*Lobar ICH will be defined as ICH involving cortical or subcortical locations and situated ≥ 1 cm from the body of the ipsilateral lateral ventricle and not originating from any of the following deep structures: thalamus, putamen, globus pallidus, caudate, or internal capsule.



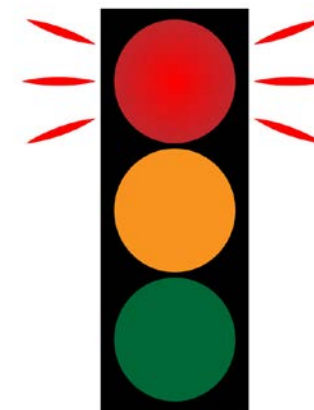
Exclusion Criteria

1. Suspected secondary cause for the qualifying ICH, such as an underlying vascular abnormality or tumor, trauma, venous infarction, or hemorrhagic transformation of an ischemic infarct.
2. History of recent myocardial infarction (attributed to coronary artery disease) or unstable angina within the previous 3 months
3. Diabetic patients with history of myocardial infarction or coronary revascularization
4. History of familial hypercholesterolemia
5. Patients receiving PCSK-9 inhibitors
6. Inability to obtain informed consent
7. Women of childbearing potential
8. Pre-morbid mRS >3
9. ICH score >3 upon presentation.



Exclusion Criteria

10. Known diagnosis of severe dementia
11. Life expectancy of less than 24 months due to co-morbid terminal conditions
12. Indication that withdrawal of care will be implemented for the qualifying ICH
13. Contraindications to continuation/resumption of statin therapy, such as significant elevations of serum creatinine kinase and/or liver transaminases, and rhabdomyolysis
14. Patients known or suspected of not being able to comply with the study protocol due to alcoholism, drug dependency, or other obvious reasons for noncompliance, such as unable to adhere to the protocol specified visits/assessments.
15. Concurrent participation in another research protocol for investigation of experimental therapy



Are you participating
in ASPIRE?



SATURN
vs.
ASPIRE

ASPIRE

- First-ever ICH
- Predominantly, deep ICH, but lobar ICH with “low-risk” cerebral amyloid angiopathy can be enrolled
 - < 5 microbleeds on MRI
 - No superficial siderosis
- Patients must have non-valvular atrial fibrillation & CHA₂DS₂-VAS_c score ≥ 2
- Patients with ICH caused by a ruptured AVM can be enrolled once AVM is secured

SATURN

- First or recurrent ICH
- Only patients with lobar ICH (any) can be enrolled
- Patients with valvular or non-valvular atrial fibrillation (regardless of CHA₂DS₂-VAS_c score) or need for oral anticoagulation can be enrolled
- Any patient with secondary ICH cannot be enrolled

You must develop an enrollment strategy for these competing trials which ensures unbiased screening of subjects to each trial

Screening Evaluation

- The following assessments should be carried out upon screening of potential candidates:
 - Neurological examination including National Institute of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS)
 - Medical history, including menstrual and gynecological history in women to identify those of childbearing potential⁺
 - Review of medications and inclusion/exclusion criteria
 - Review of head scans (CT or MRI) & any additional imaging studies to confirm the diagnosis of acute spontaneous ICH^{*}
 - Calculation of ICH volume on head CT using the ABC/2 method
- The investigators at each site will be required to maintain a screen failure log for ICH patients who are found ineligible to participate in the study. The study coordinator at each site is required to enter the screen failure data into the WebDCUTM study database within 5 days of screening.

⁺ A woman of childbearing potential is defined a pre-menopausal woman capable of becoming pregnant. This definition excludes premenopausal women with history of hysterectomy, permanent surgical sterilization, or infertility.

^{*}At a minimum, a baseline plain head CT is required to confirm the diagnosis of acute lobar ICH. The need for additional diagnostic tests, such as CTA, conventional angiography, or MRI/MRA to rule out secondary causes of ICH is encouraged and should be based on AHA/ASA guidelines

Lobar versus Non-Lobar ICH



Lobar ICH

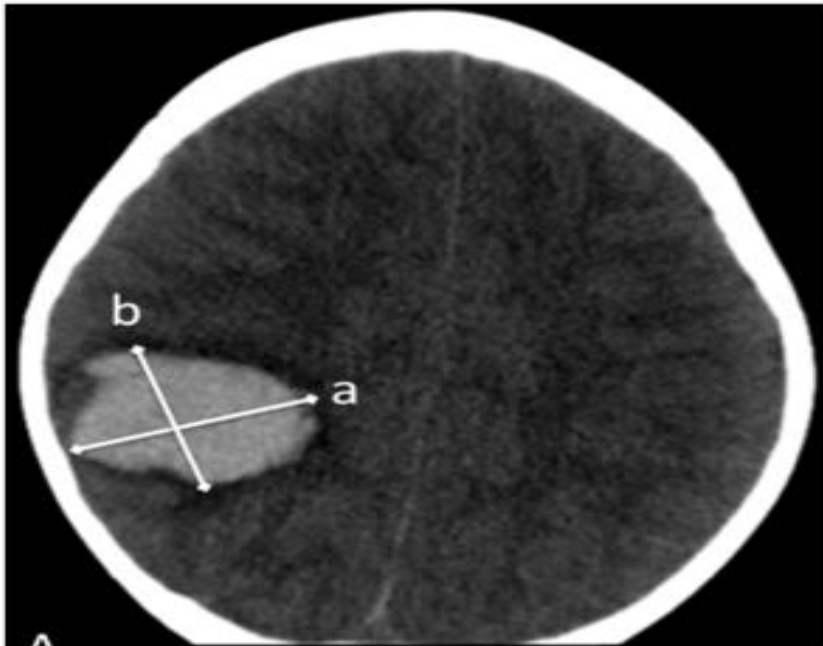
≥1 cm from the body of the ipsilateral lateral ventricle and not originating from basal ganglia or thalamus



Non-Lobar ICH

<1 cm from the body of the ipsilateral lateral ventricle and originating from basal ganglia/thalamus

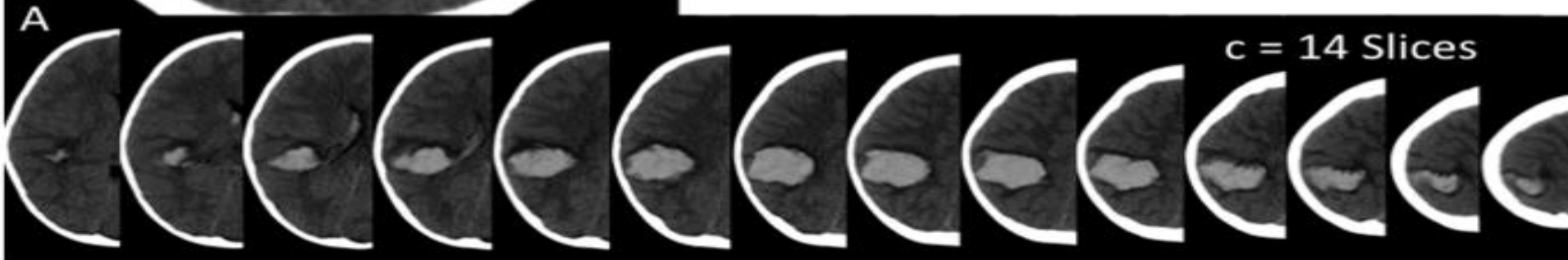
Calculation of ICH Volume: ABC/2 Method



A = Maximum length

B = Width perpendicular to A

C = Number of slices



Calculation of ICH Score

GCS Score at initial presentation	= 3-4 = 5-12 = 13-15	2 points 1 point 0 points
Age \geq 80	No Yes	0 point 1 point
ICH volume \geq 80 mL (ABC/2 method)	No Yes	0 point 1 point
IVH	No Yes	0 point 1 point
Infratentorial Location	No Yes	0 point 1 point

Obtaining Informed Consent

- IRB approved informed consent is required from all subjects or their legally authorized representative (LAR) prior to participating in the study
- Potential subjects or their LARs should be given ample opportunity to ask questions and to consider their decision. They should be given a copy of the **“Provider Study Information Sheet”** and instructed to contact their primary care physician to discuss the study further before signing the consent form
- Investigators should be available to answer the provider’s questions if needed
- If a subject or LAR expresses a sustained interest, a signed & dated informed consent will be obtained
- Patients with a known history of dementia should be excluded from self-consent
- The informed consent must be obtained by either the site PI or other members of the study team who are qualified and delegated to perform this task on the Delegation of Authority Log



Obtaining Informed Consent: Non-English speakers

- To obtain consent from non-English speaking subjects, you must have either an IRB-approved fully translated ICF or a translated short consent form in the subject's language
- The presentation of the consent must be done in the subject's language. Either the person obtaining consent must be fluent in the subject's language or an interpreter must be used
- If a short form is being used, a witness, who is fluent in both English and the subject's native language must witness the entire consent process. The study team member who obtains consent must sign the English ICF. A copy of the short form and English ICF must be provided to the participant
- Notify the project manager who will request a fully translated consent in that language to be signed by the subject within 30 days



Suggested Approach for Assessment of Capacity to Consent

UCSD Brief Assessment of Capacity to Consent (UBACC)	
1. What is the purpose of the study that was just described to you?	
Response (2 = Study investigational drug for memory)	Score
	0
	1
	2
2. What makes you want to consider participating in this study?	
Response (2 = Improve memory and attention, help others)	Score
	0
	1
	2
3. Do you believe this is primarily research or primarily treatment?	
Response (2 = Research)	Score
	0
	1
	2
4. Do you have to be in this study if you do not want to participate?	
Response (2 = No)	Score
	0
	1
	2
5. If you withdraw from this study, will you still be able to receive regular treatment?	
Response (2 = Yes)	Score
	0
	1
	2
6. If you participate in this study, what are some of the things that you will be asked to do?	
Response (2 = At least 2 of the following: answer questions, bring medications to clinic, magnetic resonance imaging, electrocardiogram, blood draw, urine testing)	Score
	0
	1
	2
7. Please describe some of the risks or discomforts that people may experience if they participate in this study. (Please describe the 2 serious risks associated with the study.)	
Response (2 = Heart problems and liver problems)	Score
	0
	1
	2
8. Please describe some of the possible benefits of this study.	
Response (2 = Societal and/or personal benefits, may help memory and attention)	Score
	0
	1
	2
9. Is it possible that being in this study will not have any benefit to you?	
Response (2 = Yes)	Score
	0
	1
	2
10. Who will pay for your medical care if you are injured as a direct result of participating in this study?	
Response (2 = The institution or hospital)	Score
	0
	1
	2

- Deviations from the answers are scored as 1 or 0
- If the answer to a question is ambiguous or uncertain, ask follow-up questions to clarify
- If the subject does not get a score of 2, you may ask the question again up to a total of 3 trials
- Make sure that the subject shows clear understanding of the issues and does not merely parrot back information

Obtaining Informed Consent: Important Reminders

- Ask the subject or LAR to provide the contact information for someone else such as a family member or caregiver that we could contact for follow up if needed. Ideally, an English-speaking person if the subject or LAR are non-English speaking
- Ask the subject or LAR for the name and contact information of the subject's Primary Healthcare Provider
- Provide the subject or LAR with the **“Study Participant Information Sheet/Card”**, which outlines what to expect during follow-up phone calls

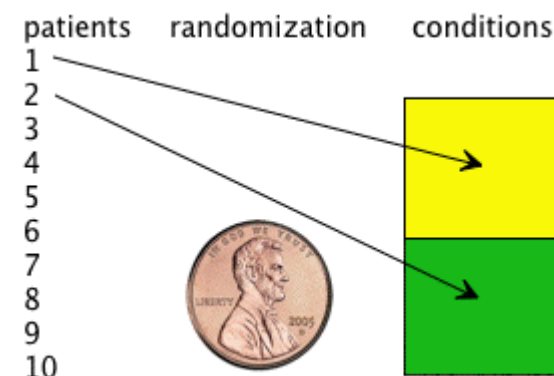


Post Enrollment Procedures and Assessments



Randomization

- Once eligibility criteria are met and informed consent is obtained, log on WebDCU™ to complete the Enrollment/Randomization Case Report Forms
- The database will allocate the subject to a treatment arm (continue vs. discontinue statin). Subjects who are assigned to continue statin will continue to take the same statin agent and dosage that they were using at the time of ICH onset
- The randomization scheme includes the following covariates:
 - Statin dose/intensity
 - Indication for statin use (primary vs. secondary prevention)
 - Use or intent-to-use anti-thrombotic drugs (anti-platelets or oral anticoagulants)
 - Baseline ICH volume (<30 vs. ≥30 ml)



Blood Sample Collection

- Once the subject is randomized, a blood sample (2 tubes) should be collected for genomic analysis
- Blood should be collected in the provided purple-top tubes
 - Universal precautions practices must be followed during blood collection & handling
 - Do not fill all the way to the way to the purple top. Only fill the vial $\frac{3}{4}$ full
 - Store the samples upright
 - Store & ship at room temperature on the day of collection. Otherwise, store in a refrigerator at 4 degrees Celsius and ship on ice within 72 hours during weekends/holidays
- If lipid profile was not done as part of standard-of-care, blood should be drawn to check lipid profile



General Care and Prohibited Medications

- The general care should conform to the AHA/ASA guidelines for management of spontaneous intracerebral hemorrhage*
- There are no restrictions on the use of concomitant medications, with the following exceptions:
 - Concurrent use of experimental or investigational therapy is not allowed during subject's participation in the trial
 - Use of PCSK-9 inhibitors is not allowed
- Use of non-statin lipid lowering agents is permitted. These include:
 - Omega-3 fatty acids (fish oil)
 - Ezetimibe

**Stroke. 2015;46(7):2032-60*

Monitoring Adverse/Outcome Events

- All participants will be followed on an ongoing basis throughout their participation in the trial for emerging adverse events
- Safety assessments will focus on detecting the following events
 - Recurrent symptomatic ICH
 - Major adverse cardiovascular events resulting in hospitalization
 - Other serious adverse events
- Assessment of these events after discharge will be performed via phone by centralized evaluators using a structured questionnaire at 1, 2, 3, 6, 9, 12, 18, and 24 months
- Assessments of Telephone MoCA, mRS, and EQ-5d QoL, verification of statin prescription refills to assess adherence, and blood pressure readings will also be conducted during these follow-up phone calls



Monitoring Adverse Events

- Remember to provide the subject or LAR with the “**Study Participant Information Sheet/Card**”, which outlines subject’s responsibilities and what to expect during follow-up phone calls
- Subjects or LARs should be instructed to notify the study investigators whenever they are re-hospitalized or experience adverse events



Reporting of Adverse Events and Outcomes by Central Evaluators

- Once the central assessors uncover any adverse event that meets the definition of a SAE such as a major adverse cardiovascular event, ischemic stroke, or recurrent ICH during the follow-up phone calls, they will enter these events into WebDCU™ within 24 hours or the following business day
- This will generate an e-mail notification to inform the local site PI & study coordinator to complete the AE CRF within 72 hours. Once completed this will trigger notification to the study statistician and independent Medical Safety Monitor to review the CRF
- The Medical Safety Monitor will make an initial assessment of the reported event(s). If the Medical Safety Monitor requests additional materials/records to assist him with event adjudication, an e-mail notification of this request will be sent to the site investigators and central assessors
- The central assessors and site investigators will coordinate their efforts to obtain the necessary materials and upload them into WebDCU™ within 7 days
- The Medical Safety Monitor will complete his final assessment within 2 business days

Reporting of Adverse/Outcome Events by the Site Investigators

- There may be cases in which participants or their caregivers notify the local site study team of the occurrence of an adverse event or any hospitalization prior to scheduled follow-up phone calls by the central assessors
- In these cases, the local team is expected to enter these events into WebDCU™ within 24 hours or the following business day
- WebDCU™ will generate an e-mail notification to inform the independent Medical Safety Monitor and the study statistician of the occurrence of the events, and will trigger review by the Medical Safety Monitor

Criteria for Premature Discontinuation of Study Participation

- The only criterion for premature discontinuation of study participation is if the subject or LAR voluntarily withdraws consent to continue participation and to complete follow up assessments
- The only pre-established criterion for premature discontinuation of statin therapy is the development of severe side effects such as marked elevations of liver function tests or impending life-threatening rhabdomyolysis
- Subjects assigned to the statin-discontinuation arm will be allowed to resume taking statins if they experience a major adverse cardio- and cerebrovascular events during their participation in the study based on the judgment of their treating physicians



Outcome Events

- The main outcome events of interest are
 - Recurrent symptomatic ICH confirmed by brain imaging
 - Diagnosis of a major adverse cardio- and cerebrovascular event after randomization in the study, which includes
 - Symptomatic ischemic stroke*
 - Symptomatic myocardial infarction**
 - Newly symptomatic arterial occlusive disease (peripheral, retinal, or carotid)
 - Revascularization procedures for coronary, carotid, or peripheral arterial disease
 - Vascular death
- A central adjudication committee blinded to treatment allocation will adjudicate all outcome events

*Ischemic strokes attributed to causes other than atherosclerosis or cardio-embolism, such as arterial dissection will be recorded separately

**Myocardial infarction due to causes other than coronary artery disease, such as due to hypovolemia or hemodynamic compromise will be recorded separately

Statistical Considerations



Interim Analyses

- A pre-specified interim analysis for overwhelming efficacy and futility will be conducted at the midpoint of the trial
- The relative risk of major adverse cardio- and cerebrovascular events and the corresponding 99% confidence interval will be evaluated in each semi-annual DSMB report (or more frequently if requested)
- If the lower bound of the confidence interval approaches (or exceeds) 1.2, the Data Safety Monitoring Board may request additional information regarding safety outcomes and may request an additional interim analysis in order to make recommendations regarding continuation/discontinuation of the study or necessary modifications.

Data Analysis

- Primary analysis will be conducted according to the intention-to-treat principle
- For subjects with a recurrent ICH, the time to event will be the time from randomization to the event
- Statistical monitoring for safety will be limited to the primary safety outcome – the occurrence of a major adverse cardio- and cerebrovascular event
- Longitudinal analyses of EQ-5D and mRS will be used to assess risks/benefits associated with discontinuation of statin drugs

Questions



SATURN@bidmc.harvard.edu

- Overall Study Principal Investigator
Magdy Selim, MD, PhD
mselim@bidmc.harvard.edu
Tel: +1-617-632-8913
- NCC Project Manager
Kimberlee Bernstein, BS, CCRP
gammk@ucmail.uc.edu
Tel: +1-513-558-3970
- BIDMC Project Manager
Sarah Marchina, PhD
smarchin@bidmc.harvard.edu
Tel: +1-617-632-8949

24/7 Clinical Hotline

For urgent questions call **+1-617-667-7000** & ask to page beeper **#39636** re: the SATURN Trial



Protocol Training Attestation



By my dated signature below, I attest that I have completed the SATURN protocol training via the following mechanism:

☐ I reviewed the SATURN protocol training slideshow

Print name: _____

Signature: _____

Date: _____

Please upload completed form to WebDCU.