A Phase 1/2a Exploratory Clinical Trial: Induced Suppression of Platelets Activity in Aneurysmal SAH Management (iSPASM)

NCT03691727

PROTOCOL VERSION DATE 14MAY2020

Clinical Protocol

Principal Investigator (PI):	David Hasan, MD
Co-Investigator (Sub-I):	James Torner, PhD, MS Lauren Allan, DO Edgar Samaniego, MD, MS Mario Zanaty, MD
Product Name:	tirofiban hydrochloride (AGGRASTAT®)
Active Ingredient:	tirofiban hydrochloride
Title of Study:	A Phase 1/2a Exploratory Clinical Trial: Induced Suppression of Platelets Activity in Aneurysmal SAH Management (iSPASM)
Study Center:	University of Iowa
Estimated number of subjects:	282 subjects (30% male, 70% female) will be recruited and enrolled in this study. 10 alternate subjects will be recruited to replace those that screen fail, drop out, or are removed from the study.
Study Period:	January 2019 until completion
Estimated date of first enrollment:	January 2019 will be the earliest day of enrollment.
IRB Approved:	05 November 2018
Estimated date of last enrollment:	We estimate that all subjects will be enrolled by June 2020.
Route of Administration:	Intravenous
Dosing Regimen:	0.10µg/kg/min (actual weight) within 48 hours from the angiogram and at least 12 hours post external ventricular drain (EVD), continuous for a total of 7 days.

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SUMMARY OF CHANGES

Section	Change
14 May 2020	**Version 3.0 to 4.0**
Cover page	Updated amendment version and date.
XIII	Defined adverse events and clarified AE collection procedures.

SUMMARY OF CHANGES

Section	Change
19 December 2019	**Version 2.0 to 3.0**
Cover page	Updated amendment version and date.
X	Added phone option for 6 month follow up and 1 year follow up.
XI	Added option for phone call at 6 month and 1 year follow up.
XIII	Defined adverse events and clarified AE collection procedures through new section, Adverse Event Reporting.
XXII	Corrected numbers of subjects to better reflect changes made in randomization in version 2.0.

SUMMARY OF CHANGES

Section	Change
19 April 2019	**Version 1.3 to 2.0**
Cover Page	Updated amendment version and date and replaced h with hours. Grammatical error correction.
Entire Document	Updated numbering to allow this protocol to become a stand-alone document.
IV.	Changed randomization to 2:1
V.	Grammatical error correction.
VI.	Updated age from 80 to 85.

VIII.	Updated Inclusion criteria to update age, clarify, to more closely match SOC and to remove exclusion duplication.
IX.	Updated exclusion criteria to clarify and to more closely match SOC procedures.
X.	Updated to allow up to 2 passes during EVD placement, add clarification and to more closely match SOC procedures.
XI.	Renamed Randomization Visit to Day One Visit, added +/- 3 days to Discharge Visit MRI and changed CBC to Blood Draw with explanation.
XII.	Grammatical error correction
XIII.	Updated wording in adverse event collection to reflect the collection of adverse events through not only interaction with the subject but also the collection of events through the EMR.
XIV.	Clarified how access is given.
XVI.	Removed unneeded language.
XVIII.	Grammatical error correction.
XX.	Updated language to reflect that Safety Stop Points would be “per DSMB Charter”.
XXIII.	Grammatical error correction.

SUMMARY OF CHANGES

Section	**Change**
05 January 2018	**Version 1.2 to 1.3**
Cover page	Updated amendment version, date and corrected dosing regimen
X.II	Revised dose

SUMMARY OF CHANGES

Section	**Change**
10 October 2018	**Version 1.1 to 1.2**

X.1	Added new investigators, updated percentages of males and females to more accurately represent clinical presentation, updated study timeline, added placebo.
X.3	Updated approval
X.5	Trial Design: Updated to double blind
X.8	Updated recruitment schedule
X.9	Updated inclusion criteria so that it more closely matched updated SOC procedures.
X.10	Updated exclusion criteria for clarity and to include additional criteria.
X.11	Schedule of events: Updated to include placebo, modify schedule, updated SOC procedures and clarify.
X.12	Schedule of events: Updated to include Raymond-Roy score, additional 30-day follow-up phone call and CBC.
X.13	Updated IV risk and added risk of MRI to include claustrophobia.
X.14	Adverse Event Reporting: Updated to include SAE and AE monitoring and reporting.
X.16	Deleted time frame information.
X.17	Updated secondary endpoints with new follow up times, clarified language.
X.20	Data Safety Monitoring Board (DSMB): Updated with DSMB Charter
X.21	Clarified endpoints and added additional endpoints.
X. 22	Added unmasking and safety section.
X. 23	Clarified language in the statistical design plan
X. 24	Created a new section for definitions.

I. Statement of Compliance:

This study will be conducted in compliance with the protocol, Good Clinical Practice and the applicable Food and Drug Administration and other Department of Health and Human Services regulatory requirements.

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection and Good Clinical Practice training.

II. IRB Oversight:

Human Subjects Office / IRB
J. Andrew Bertolatus, MD
Hardin Library, Office 105
600 Newton Rd
Iowa City, IA 52242
FWA#: FWA00003007
Voice: 319-335-6564
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Email: irb@uiowa.edu

IRB ID# 201805823
Approved 05 November 2018

III. Location of Study Procedures:

University of Iowa Hospitals and Clinics
200 Hawkins Drive
Iowa City, Iowa 52242

IV. Trial Design:

Phase 1/2a, single center, randomized 2:1, double blind, Aggrastat vs. placebo.

V. Main Hypothesis:

Long term use Aggrastat (7 days) is safe in subjects with aneurysmal subarachnoid hemophage (aSAH) and has minimal symptomatic hemorrhagic risk conversions associated with ventriculostomy/VP-shunt placement.

Aim 1: To test the above hypothesis, we will assume that:

A) The risk of symptomatic hemorrhage secondary to ventriculostomy/VPS placement during the course of Aggrastat use is within 10% difference when compared to control.

B) The risk of asymptomatic hemorrhage secondary to ventriculostomy/VPS placement during the course of Aggrastat use is within 30% difference when compared to control.

VI. Main Screening Criteria:

We will recruit men and non-pregnant women of any ethnic background between the age ≥ 18 and ≤ 85 years that have been treated for SAH caused by intracranial aneurysm.

VII. Screening/Recruitment procedures:

The study team will be notified by the neurosurgery resident on call when a potential subject is seen in the ED for a possible aSAH. Study team will review potential subject's chart for possible inclusion/exclusion criteria. This pre-screening is done so that potential subjects and their families are not approached until the study team reviews and verifies that it would appear that the subject may qualify.

Patients with aSAH will be taken to the OR for EVD placement and admitted to the SNICU. An angiogram is performed within 24 hours of admission. If following angiography, the patient meets inclusion criteria, the study team will approach the potential subject and/or their Legally Authorized Representative (LAR) and tell them that the patient may qualify for a study and ask if they are interested in hearing about the study. If the potential subject and/or their LAR are interested, the study will be explained to them in detail. They will be encouraged to ask questions and talk it over with the treating physician and family members.

If the potential subject and/or their LAR would like the potential subject to participate, one of the members of the study team will go over the consent form with them, answering any questions they may have as the study team goes through the consent form. Once they have reviewed the entire consent form the study team will ask them once again if they have any questions. Once any questions are answered they can choose to sign the consent form if they choose to participate or the LAR chooses to have the potential subject participate. The potential subject or LAR will have 24 hours post angiography with embolization to decide if they would like to participate.

To avoid any coercion all subjects are offered the opportunity to talk with the treating physician or family prior to signing a consent form. Study participation has no influence on the standard of care they would otherwise receive for their disease process. Once consent is obtained, the patient will be randomized to control vs. placebo. The LAR or subject can withdraw from the study at any time if he/she decides to.

VIII. Inclusion Criteria:

- Age ≥ 18 and ≤ 85 years
- Hunt and Hess scale ≤ 4 at time of admission or following EVD placement.
- CT showing modified Fisher grade 1-4 aSAH on admission.
- The Modified Fisher CT rating scale: Grade 1 (minimal or diffuse thing SAH without IVH); Grade 2 (minimal or thin SAH with IVH), Grade 3 (thick cisternal clot without IVH), Grade 4 (thick cisternal clot with IVH) [From: Claassen J et al. Effect of cisternal and ventricular blood on risk of delayed cerebral ischemia after subarachnoid hemorrhage: The Fisher scale revisited. Stroke 2001; 32:2012-2020.]
- Placement of EVD on admission.
- Aneurysmal SAH confirmed by the angiography obtained during the coil embolization procedure.
- Diagnosis of aSAH occurred < 24 hours prior to presentation at the treating facility..
- Initiation of aneurysm securement procedure occurred </= 24 hours from admission to the treating facility.
- All aneurysm(s) suspected to be responsible for the hemorrhage or potentially responsible for the hemorrhage must be secured in the following manner prior to enrollment:
    - Endovascular Coil Embolization with a post-embolization Raymond-Roy Score of 1 (Complete) or 2 (Residual Neck)
- Ability to screen the patient and obtain head CT, CT perfusion, and CCTA on admission, a head CT following EVD placement, during EVD weaning period and following VP shunt placement.
- No evidence of a significant new focal neurological deficit after the angiogram, including monoparesis / monoplegia, hemiparesis / hemiplegia, or receptive, expressive or global aphasia. Minor cranial nerve defect without any other new findings is permissible. The treating physician should use their best clinical judgment as to whether a significant neurological decline has occurred due to the procedure.
- Patient or their Legally Authorized Representative (LAR) has provided written informed consent.

IX. Exclusion Criteria:

- Angio-negative SAH, defined as a subarachnoid hemorrhage with an angiogram that does not show a related intracranial hemorrhage.
- A likely hemorrhagic event preceding the SAH ictus, due to the increased risk of early vasospasm. Prior sentinel headache with negative CT or prior sentinel headache where the patient did not seek medical attention does not exclude the patient.
- Surgical clipping of the ruptured aneurysm or any non-ruptured aneurysm on the same admission prior to enrollment.
- SAH not caused by aneurysm rupture or traumatic, mycotic, blister or fusiform aneurysm repaired by stent and/or flow diverter.
- Any intracranial stent placement or non-coil intra-aneurysmal device (i.e., stent- assisted coiling with Neuroform, Enterprise, LVIS, LVIS Jr, Barrel Stent, Pulse Rider) where the stent device is implanted to treat the ruptured aneurysm.
- A medical diagnosis that requires continuous use of clopidogrel, ticagrelor or tirofiban during study drug infusion.
- Antiplatelet therapy using clopidogrel, tricagrelor or tirofiiban during the endovascular procedure that continues > 24 post embolization.
- Multiple aneurysms where one may have been untreated and a potential etiology for rupture. Femoral arteriotomy stick above the inferior epigastric artery OR angiographic, CT, or clinical evidence of an arteriotomy related retroperitoneal hematoma or large flank hematoma. A stable groin hematoma is not an exclusion.
- Thrombocytopenia (platelet count less than 100,000 - assuming clumping has been ruled out as a cause), confirmed active disseminated intravascular coagulation (DIC) at the time of enrollment OR a documented history of coagulopathy or bleeding diathesis.
- New parenchymal hemorrhage or new infarction larger the 15cc in volume (clinically significant), or worsening midline shift as seen on the post coiling pre-enrollment head CT when compared to baseline admission head CT. New hyperdensity on CT scan related to contrast staining is not an exclusion.
- Patient developed SAH-induced cardiac stunning prior to enrollment, with an ejection fraction< 40%
- Thrombolytic therapy within 24 hours prior to enrollment (rtPA, urokinase, etc.)
- Concurrent significant intracranial pathology identified prior to enrollment, including but not limited to, Moyamoya disease, high suspicion or documented CNS vasculitis, severe fibromuscular dysplasia, arteriovenous malformation, arteriovenous fistula, significant cervical or intracranial atherosclerotic stenotic disease (≥70%), or malignant brain tumor.

- Known seizure or epilepsy disorder (diagnosed prior to this aSAH diagnosis) where anti-epileptic medication was previously taken by the patient or have been recommended to be taken by the patient. Childhood seizures that have resolved and no longer require treatment are not part of this exclusion criteria

- Serious co-morbidities that could confound study results including but not limited to: Multiple Sclerosis, dementia, severe major depression, cancer likely to cause death in 2 years, multi-system organ failure, or any other conditions that could cause any degree of cognitive impairment.

- Immunosuppression therapy of chronic corticosteroid usage.

- Remote history of previous ruptured cerebral aneurysm.

- History of gastrointestinal hemorrhage or major systemic hemorrhage within 30 days, hemoglobin less than 8 g/dL on admission, INR ≥1.5, severe liver impairment as defined as AST, ALT, AP,GGT > 2 x normal

- Creatinine clearance <30 mL/min.

- Major surgery within 30 days with contra-indication to antiplatelet therapy Currently pregnant.

- Contraindication for MRI

- Contra-indication to antiplatelet tirofiban:

    a. active internal bleeding or a history of bleeding diathesis within the previous 30 days
    b. A history of thrombocytopenia following prior exposure to AGGRASTAT
    c. history, symptoms, or findings suggestive of aortic dissection
    d. acute pericarditis

- Actual Body Weight >150kg (due to the lack of safety data)

- 2 or more passes for the ventricular catheter at time of placement.

X. Schedule of events:

- Subject is evaluated in the Emergency Department (ED) using:
  - Detailed neurological exam.
  - Hunt and Hess and Fisher grade.

- Subject is evaluated for aSAH and hydrocephalus using non-contrasted Head CT, CT-Perfusion, and CTA

- Prior to angiography and embolization, MAP > 65 but <80.

- Research team notified of potential patient and begins pre-screening*

- If subject needs EVD for hydrocephalus, subject will be transferred to the operating room for placement of EVD (one pass to minimize brain trauma):
  - No bed side placement of EVD.

- EVD is placed in operating room using our strict protocol:
  - Perforator to make burr hole.
  - Coagulation of the dura and cortical surface.
  - Ghajar guide to place ventricular catheter.
  - If >2 passes, then subject is excluded. *
  - Following placement of EVD, admit to SNICU.
  - Re-evaluation of Hunt Hess score post EVD placement *
  - Non-contrast head CT after procedure within 6 hours to confirm placement.

- If no hydrocephalus, then admit to SICU. If an EVD is not placed, subject would not be enrolled due to not meeting the inclusion criteria.

- Aneurysm coiling within 48 hours from diagnosis and within 24h from admission.:

- Review inclusion/exclusion criteria, approach potential subject and LAR and obtain informed consent. Informed consent should be obtained within 24 hours post angiography with embolization.*.

- Subjects are randomized once consent is obtained. *
- A post-angiogram MRI is obtained within 48h from the angiogram following consent*.

- Initiate Aggrastat/placebo (0.9% NS) infusion (0.10µg/kg/min based on actual body weight) within 48h from the angiogram but at least 12-hours after EVD placement following MRI. (If unable to administer within this timeframe, then the subject is withdrawn). *

- Subcutaneous Heparin per standard of care (SOC) for DVT prophylaxis.

- Subject will have daily CBC to monitor hemoglobin and platelet counts on days 1-7 of Aggrastat/placebo infusion administration.

- Subject will have Neuro Exam completed daily while hospitalized as SOC (information recorded by study from EMR)

- If the subject develops a CrCl <30 mL/min, will decrease the dose of Aggrastat/placebo infusion to 0.05mcg/kg/min. *

- After angiography with embolization, MAP to be maintained and adjusted per SOC.

- Patients will be started on PO Nimodipine per SOC

- Follow SAH precautions: limited visitors, darkened room, no caffeine, no television.

- If neuro-exam changes, consult neurosurgery, neuro-IR and critical care team per standard of care. If patient develops vasospasm, then initiate vasospasm protocol (rescue therapy) per standard of care.

- Continue vasospasm management using rescue therapy for 5-7 days.

- Once subject stable, wean off EVD. This will involve performing at least one head CT.

- If subject needs VP shunt placement, then the following protocol is followed:
  - **Stop Aggrastat/placebo infusion for 6 hours prior to scheduled surgery (if time of placement is during the 7-day course of Aggrastat). ***
  - Use same burr hole.
  - Either soft past using the old track or use Ghajar guide to place ventricular catheter.
  - Use monopolar foe skin incision and dissection in the abdomen (may consult general surgery to place abdominal portion laparoscopically). Head CT with shunt series to be performed following VP Shunt Placement.
  - Resume Aggrastat/placebo use 12 hours post procedure but no later than within48 hours until the end of 7 days from initial use. Do not resume if 7-day course is complete. *

- Second MRI prior to discharge *

- 30 Day post last infusion date follow-up phone call to collect adverse events. *
  - 6 weeks follow up (standard of care). mRS score. *
  - Neuro Exam Check List (information can be taken from EMR) *

- 6 months follow up visit (standard of care):
  - Lawton instrumental activities of daily living (IADL). *
  - Quality of Life in Brain Injury - Overall Scale (QOLIBRI-OS). *
  - mRS score. *
  - Neuro Exam Check List (information can be taken from EMR) *

    - Return to Work

- One-year follow-up (standard of care):
    - Lawton instrumental activities of daily living (IADL). *
    - Quality of Life in Brain Injury - Overall Scale (QOLIBRI-OS). *
    - mRS score. *
    - Neuro Exam Check List (information can be taken from EMR) *
    - Return to Work

If the 6-month or one-year follow-up visits are not scheduled per standard of care or standard of care visit occurs outside the study visit window, the following will occur:

- 6-month follow up via phone call*:
    - Lawton instrumental activities of daily living (IADL)*.
    - Quality of Life in Brain Injury - Overall Scale (QOLIBRI-OS) *.
    - Return to Work*
    - Adverse events*

- One-year follow-up via phone call*:
    - Lawton instrumental activities of daily living (IADL)*.
    - Quality of Life in Brain Injury - Overall Scale (QOLIBRI-OS) *.
    - Return to Work*
    - Adverse events*

In addition, if the standard of care visit does occur but the questionnaires could not be done, a member of the study team will contact the subject via phone to complete the questionnaires and collect adverse events.

* Indicates research only procedure.

Aggrastat/Placebo will be stopped if one of the following occurs:

1) Symptomatic intracranial hemorrhage
2) Asymptomatic intracranial hemorrhage
3) Thrombocytopenia <20,000
4) Any emergent or urgent procedure is necessary.
5) Any new symptomatic hemorrhage necessitating transfusion of more than 2 units of packed red blood cells.
   Gastrointestinal bleed
   Retroperitoneal bleed
   Menorrhagia

   Unmasking: Aggrastat/placebo may be discontinued, and subject may be unblinded. If this occurs, subject will not resume Aggrastat/placebo.

XI. Schedule of Events Table:

Event	Screening Visit (Day-1)[b]	Day 1[b]	Day 2,3,4,5,6,7	Discharge Visit	30-day Follow-Up Phone Call	6 Week Follow Up Visit (+/- 30 days)	6 Month Follow Up Visit (+/- 30 days)[g]	One Year Follow Up Visit (+/- 30 days)[g]
Informed Consent	X							
Medical History	X							
Medical Record Review	X	X	X	X		X	X	X
Neuro Exam	X	X	X	X		X	X	X
Vital Signs[a]	X	X	X	X		X	X	X
Pregnancy Test on WOCBP[a]	X							
Review of inclusion/exclusion criteria and lab results to confirm subject eligibility	X	X	X					
Administration of IP		X	X					
Review of Concomitant Medications	X	X	X	X		X	X	X
Adverse events monitoring		X	X	X	X	X	X	X
MRI	X[b]			X[f]				
Blood Draw[e]	X	X	X	X				
mRS score documentation						X	X	X
IADL							X	X
QOLIBRI-OS							X	X
Return to Work							X	X
Raymond-Roy Score	X[d]							

a. Standard of care but study team will document.
b. Screening and Day 1 visits can occur on the same day.
c. Post-angio MRI can occur within 48h from the angiogram and must be done prior to administration of IP
d. Raymond-Roy score will be collected during surgery and at any other time points when it is collected as SOC
e. Platelet count from the CBC Panel and creatinine from the Metabolic Panel will be monitored for study purposes
f. MRI can be performed +/- 3 days of discharge
g. If these visits do not occur as standard of care, follow-up phone calls will be done to collect adverse events and the IADL and QOLIBRI-OS questionnaires will be done by phone. Information regarding the subject's return to work will also be collected during that phone call.

XII. Possible Risks of the Study:

AGGRASTAT® (tirofiban hydrochloride) injection, for intravenous use Initial U.S. Approval: 1998 is approved as a platelet aggregation inhibitor indicated to reduce the rate of thrombotic cardiovascular events (combined endpoint of death, myocardial infarction, or refractory ischemia/repeat cardiac procedure) in patients with non-ST elevation acute coronary syndrome (NSTE-ACS). It is currently not approved for decreasing the risk of clinical vasospasm and delayed ischemic changes in patients who have been treated for SAH. The most common risk associated with using AGGRASTAT® (tirofiban hydrochloride) intravenously is bleeding and thrombocytopenia. Rare adverse reactions include: edema/swelling, pelvic pain, vasovagal reaction, bradycardia, coronary artery dissection, leg pain, dizziness, sweating and severe allergic reactions including anaphylactic reactions.

Concomitant use of fibrinolytics, anticoagulants and antiplatelet drugs increases the risk of bleeding.

Patients with moderate to severe renal insufficiency have decreased plasma clearance of AGGRASTAT.

The study is designed to reduce these risks by careful pre-screening, monitoring and follow up visits. If subject requires additional VP shunt placement, Aggrastat/placebo will be discontinued for 6 hours prior to scheduled surgery and resumed 12 hours post-procedure.

The standard risks of IV injection include: local reactions, fever, local tenderness, abscess, tissue necrosis or infection at the site of injection, venous thrombosis or inflammation of the vein (phlebitis). The standard risks of phlebotomy include discomfort upon placement of an IV catheter, bruising at the site of blood draw, hypersensitivity to adhesives or surgical tape, irritation at the catheter site, as well as a small risk of infection. It is also possible that subjects may feel lightheaded, dizzy, or nauseated during or after the IV placement.
The risk of the loss of confidentiality: To reduce risk of a loss of confidentiality, precautions will be taken to ensure privacy. The PI and study team will maintain appropriate medical and research records for this study, in compliance with ICH E6 GCP, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Research records generated in this study will be stored in file cabinets in a locked room and/or on a secure electronic database. Only authorized study team at the sites will have access to the data. Imaging collected during the study will be identified by a subject number, IRB protocol number, and date of collection.

The risk of MRI: Subject may feel uncomfortable inside the MRI if they do not like to be in closed spaces (claustrophobia).

XIII. Adverse Event Reporting:

The University of Iowa requires Investigators to collect and report to the University of Iowa IRB if any of the following occur:

- An unanticipated problem involving risks to subjects or others is any event or problem that:
    1) was unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB- approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied AND
    2) suggests that the research places subjects or others (those not directly involved in the research such as research staff or family members) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized AND
    3) is related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research).
    4) Serious adverse drug event (either expected or unexpected) occurring in a UI subject
    5) If a subject is enrolled by U/VAHCS investigators, the investigator must report to the UI IRB either serious adverse drug events or unexpected adverse drug events. By definition, these events must be associated with the use of the drug.
    6) An unexpected adverse drug event is any adverse drug experience (associated with the use of the drug), the frequency, specificity, or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information provided to the subjects and the IRB
- A serious adverse drug event is any adverse drug experience (associated with the use of the drug) occurring at any dose that results in any of the following outcomes:
    1) Death
    2) Life-threatening adverse drug experience
    3) Inpatient hospitalization or prolongation of existing hospitalization
    4) A persistent or significant disability/incapacity
    5) A congenital anomaly/birth defect
    6) Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when,

based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

- Receipt of new information

  During the course of a study, researchers may become aware of new information that would impact a subject's decision to participate or continue participating in the research study. For example, interim analyses of data may identify a trend which impacts the safety of subjects or may identify early efficacy (benefit) of one of the interventions under study. In addition, results from other research studies or changes in standards of practice or care may affect conduct of a study and would need to be communicated to research subjects.

- Noncompliance

  Noncompliance is a failure to follow the federal regulations with respect to protection of human subjects in research or failure to follow the determinations of the IRB with respect to conduct of the research as approved by the IRB.

Once per year, the IRB is required to review and approve all non-exempt research projects at intervals appropriate to the degree of risk, but not less than once a year. This is called "continuing review." Continuing review for non-exempt research is required to occur as long as the research remains active for long-term follow-up of the research subject, even when the research is permanently closed to the enrollment of new subjects and all subjects have completed all research-related interventions and to occur when the remaining research activities are limited to collection of private identifiable information.

Adverse Event Collection:

The clinical research team is responsible for collecting and recording the research data. As the results are collected, all adverse events will be identified after an informed consent is signed by the subject or their legally authorized representative (LAR) and the medication is initiated.

Throughout the study, the 30-day phone call and during all follow-up visits, in addition to the medical chart review, adverse events are to be elicited by the investigator (or designate) by asking the subject non-leading questions. All AEs and SAEs will be reported to the principal investigator (PI) and the PI will determine the final relationship of the event to the investigational product.

AGGRASTAT® (tirofiban hydrochloride) has a half-life of approximately 2 hours. Therefore, and according to the pharmacokinetics, the drug will be cleared by 24 hours. Therefore, any events after 24 hours are very unlikely related to the drug.
All AEs and SAEs will be recorded following the initiation of the study drug until 5 days after the last dose of study medication

Starting 5 days after the last dose of study medication and up to the 30 day follow up, only the following adverse events of special significance and primary serious adverse events associated with Aggrastat will be recorded:

Adverse events of special significance are:

- Bleeding events
- Edema/swelling
- Pelvic pain
- Vasovagal reactions
- Bradycardia
- Coronary artery dissection
- Leg pain
- Dizziness
- Sweating
- Allergic reaction

The primary serious adverse events associated with Aggrastat are: thrombocytopenia.

Following the 30 follow up, only primary serious adverse events (SAEs) will be recorded.

Occurrence of adverse events will be monitored throughout the trial and will cover all randomized subjects. Trial subjects will be provided with a 24-hour telephone number to contact trial personnel in case of an untoward reaction after hospital discharge

Adverse events that meet criteria of serious, unexpected, and attributed (possible, probably, or definite) to the IP must be reported to the FDA.

This study will also be monitored by a Data and Safety Monitoring Board. For non-serious adverse events, documentation must begin from the first day of study drug and continue through the 30-day follow-up phone call. Routine adverse events will be reported by submission of an adverse events log to the DSMB at the time of the DSMB review. Serious adverse events occurring during active therapy will require notification to the DSMB within 1 business day of learning of the event. The SAE capture window will be from the first administration of IP through the 30-day follow-up phone call. Serious adverse events are reportable to the DSMB within 1 business day of learning of the event if the adverse event meet the criteria of serious, unexpected, and attributed (possible, probably, or definite) to the IP.

XIV. Data Management

The following people/agencies may have access to subject data/records:

- Study team
- Federal government regulatory agencies
- Auditing departments of the University of Iowa
- University of Iowa IRB
- Sponsor and/or its representative

To protect confidentiality, we will assign each subject a study ID. All records will be in a locked cabinet in a locked office or password protected computer system. Data and records will be managed as follows:

- Paper/hard copy records (hard copy surveys, questionnaires, case report forms, pictures, etc.) - Whenever possible, subject identifying information will be blacked out on all paper or hard copy records and replaced with the subject's unique study identifier. Paper records will be stored in a locked file cabinet in the study team's locked office.
- Electronic records (computer files, electronic databases, etc.) – All electronic data bases will only be accessed by the study team and available only with a username and password. Study team members will be granted access by the PI.
- After the completion of the study, all identifiable information will be destroyed according to the University of Iowa’s IRB standards, as soon as possible.

XV. Primary End points:

- Hemorrhagic changes evident on head CT and/or MRI. Specifically, the rate of "Symptomatic Bleeding" and "Asymptomatic Bleeding" [Designated as safety stop point]

XVI. Secondary End points:

- mRS at follow-up visits. Relative frequency of "good outcome" as defined by dichotomized mRS score 0-2
    - Time Frame: 6-week, 6-month and 1-year follow-up visits.
- Incidence of radiographic cerebral vasospasm: Incidence of moderate and severe radiographic cerebral vasospasm (catheter angiogram, CTA, MRA) Incidence of symptomatic cerebral vasospasm and/or DCI Delayed Cerebral Ischemia requiring rescue therapy (Rescue therapy = vasopressors or endovascular therapy for the purposes of reversing clinical vasospasm.
- Incidence of CT or MRI imaging demonstrating cerebral vasospasm
- Return to work status
    - Time Frame: 1-year follow-up visit.
- Lawton instrumental activities of daily living (IADL)
    - Time Frame: 6 month and 1-year follow-up visits.
- Quality of Life in Brain Injury - Overall Scale (QOLIBRI-OS)
    - Time Frame: 6 month and 1-year follow-up visits.

XVII. Payment for Participation:

Subjects will not receive payment for participating in this study. All study related medication and study procedures will be paid for by the study.

XVIII. Subject Safety:

- To minimize risks all subjects are carefully pre-screened and screened trying to identify any factors that could contribute to increased risk.
- All testing is completed at University of Iowa Hospitals and Clinics by a very experienced and well-trained staff and monitored by the Principal Investigator.
- All confidential information is kept in locked offices and password protected computers only available to study team members.
- The participant has contact information and study team members available 24/7.

XIX. Data Safety Monitoring Board (DSMB):

A DSMB will be convened to assess the progress of the clinical study, the safety data, and critical efficacy endpoints. Details regarding the DSMB can be found in the DSMB Charter Version 7.0 dated 03 December 20182018.

XX. Safety stop-points (per DSMB charter):

- The risk of symptomatic intracranial hemorrhage is ≥ 10% when compared to control.
- The risk of asymptomatic intracranial hemorrhage is ≥ 30% when compared to control.
- The rate of thrombocytopenia (platelets <20,000) is ≥ 10% when compared to control.
- The rate of hemorrhagic bleeding requiring > 2 units of red blood cells transfusion is ≥ 10% when compared to control (ex: GI, retroperitoneal, etc).
- The threshold of 20% as maximum allowable symptomatic hemorrhage per each quarter. If the threshold is reached, the study will be stopped, and all adverse events are reviewed.
- If all the symptomatic hemorrhage reported is due specifically to the agent being tested, then the DSMB will make recommendation to stop the study.

XXI. Unmasking and safety:

A. Stopping the medication.

1) Symptomatic intracranial hemorrhage
2) Asymptomatic intracranial hemorrhage
3) Thrombocytopenia <20 000
4) Any new symptomatic hemorrhage requiring > 2 units packed red blood cells (ex: GI, retroperitoneal, etc).
5) Any emergent or urgent procedure.

B. Unmasking.

If any patient required an emergent surgery or if any information regarding the IP is needed for clinical decision, we will initiate the unmasking protocol and the IP will be stopped. Furthermore, if surgery was required and the patient turned out to be on Aggrastat, the medication is stopped for 6h. For interventions that cannot be postponed for 6h, platelet transfusion and fresh frozen plasma will be given to subjects that have been unblinded and in the process it was determined that the subject was randomized to receive Aggrastat.

XXII. Statistical design plan:

The risk of symptomatic hemorrhage is expected to be within 10% difference when compared to control.

The risk of asymptomatic hemorrhage is expected to be within 30% difference when compared to control.

Given the above assumptions, the sample size calculation for the safety endpoint: the safety outcome will be symptomatic or asymptomatic bleeding during the hospital stay with an expected average of 3 weeks. We expect to observe 5% of the patients in the placebo group to experience the symptomatic or asymptomatic bleeding during the hospital stay. We assume the event rate in the dual antiplatelet therapy group to be not higher than 15%. With a two-sided chi-square test with 0.05 type I error rate, the sample size of 212 Aggrastat and 70 placebo patients (282 patients total) would allow us to compare this safety outcome between groups with 80% power.

XXIII. Definitions:

1. Symptomatic cerebral vasospasm defined as: clinical deterioration (focal neurological impairment;) in the setting of an angiographic vasospasm or a radiographic vasospasm based on CT perfusion of the corresponding territory, requiring rescue therapy.

1.1. Focal neurological impairment: such as hemiparesis, aphasia, apraxia, or neglect), or a decrease of at least 2 points on the Glasgow coma scale (either on the total score or on one of the components) This should: a) last for at least 1 hour, b) not be apparent immediately after aneurysm occlusion, and c) not to be attributed to other causes by means of clinical assessment, CT, or MRI scanning of the brain, and appropriate lab studies)

1.2. Radiographic vasospasm: Increase in mean transient time, decrease in cerebral blood flow with preservation of cerebral blood volume in the affected area compared to normal

1.3. Angiographic vasospasm:

1.3.1 Mild vasospasm: decrease in vessel diameter by ≤ 25% of normal artery diameter.

1.3.2. Moderate vasospasm: decrease in vessel diameter > 25% but ≤ 50% of normal artery diameter.

1.3.3. Severe vasospasm: decrease in vessel diameter > 50% of normal artery diameter.

2.Delayed Cerebral Ischemia: Defined as a symptomatic vasospasm with cerebral infarct.

2.1. Cerebral infarction: presence of infarction on either: 1) CT and/or MRI 24 hours post procedure and not attributable to endovascular procedure (punctate infracts). Hypodensities on CT imaging resulting from EVD or intraparenchymal hematoma should not be regarded cerebral infarction from DCI:

2.1.1. Infarct on non-contrasted head CT: hypodensity ≥ 1 x 1 cm and not attributable to EVD/shunt, intraparenchymal hematoma, and/or endovascular procedure

2.1.2. Infarct on MRI: area of the brain that appears on MRI as: 1) hyperintense area of the brain on Diffusion weighted Image (DWI) not attributable to infections, cysts, abscesses, or trauma, 2) same area as hyperintense area on T2FLAIR images, and 3) hypointense on apparent diffusion coefficient (ADC) maps.

3.Symptomatic hemorrhage from ventriculostomy/VPS: Any hemorrhage evident on non-contrasted head CT and/or MRI that is larger than ≥ 3cm in its largest diameter and associated with the track of the catheter used for EVD or VP shunt.

4.. Asymptomatic hemorrhage from ventriculostomy/VPS: Any hemorrhage evident on non-contrasted head CT and/or MRI that is larger than < 3cm in its largest diameter and associated with the track of the catheter used for EVD or VP shunt.

5. New Symptomatic hemorrhage: any new intracranial hemorrhage greater than 3 cm in the largest diameter, leading to worsening neurological exam, re-admission to the ICU, requiring surgery, associated with new-onset seizure, and/or leads to an increase stay in SNICU or hospitalization.

6. Worsening existing hemorrhage: Interval increase in the size of the hyper density on the CT scan for >2mm.

7. Angio-negative Vasospasm: Clinical deterioration (focal neurological impairment) without evidence of radiographic vasospasm, deemed by the treating physician team as due to vasospasm after ruling out other causes and requiring rescue therapy.

8. New asymptomatic hemorrhage: interval development of a new hemorrhage, < 3cm in the largest diameter, that is not causing any neurological impairment.