

A Double-blind, Randomized, Placebo Controlled
Pilot Trial to Evaluate the Safety and Efficacy of
Vorapaxar in Maturation of Arteriovenous Fistulae for
Hemodialysis Access

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Section #1 - MISP Protocol Identification

Study Title:	A double-blind, randomized, placebo controlled pilot trial to evaluate the safety and efficacy of vorapaxar in maturation of arteriovenous fistulae for hemodialysis access (VorapAccess)
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Section #2- Core Protocol

2.1 Objectives & Hypotheses

Objectives:

1. To determine if vorapaxar safely improves arteriovenous (AV) fistula functional maturation when administered during the maturation process compared with placebo.
2. To determine if vorapaxar safely improves AV fistula patency, allowing for secondary procedures to aid in fistula maturation compared with placebo.
3. To determine if vorapaxar safely facilitates successful cannulation of AV fistulas for hemodialysis compared with placebo.
4. To determine the safety profile of vorapaxar for patients requiring hemodialysis.

Hypotheses:

1. Vorapaxar initiated two days following AV fistula creation will result in improved fistula functional maturation without increased risk of bleeding or other major adverse events.
2. Vorapaxar initiated two days following AV fistula creation will result in improved fistula patency and will increase the utility of secondary procedures to aid in fistula maturation, without increased risk of bleeding or other major adverse events.
3. Vorapaxar initiated two days following AV fistula creation will facilitate successful cannulation of AV fistulas for hemodialysis without increased risk of bleeding or other major adverse events.

2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data

Background

End-stage renal disease affects nearly 500,000 persons in the US and more than 2 million persons worldwide. In the US and most developed countries, hemodialysis is the predominant dialytic modality. While effective at sustaining life for most patients, hemodialysis rarely restores health. Roughly one in five patients on dialysis die each year; patients who survive experience poor functional status, impaired physical and cognitive function and severely impaired health-related quality of life. Moreover, the cost of the ESRD program exceeds \$40B in the US annually (1).

Hemodialysis vascular access is often referred to as the 'Achilles Heel' of dialysis care. The Brescia-Cimino (radiocephalic end-to-side) fistula is considered to be the gold standard vascular access (2); upper arm arteriovenous fistulae are often created instead. Polytetrafluoroethylene (PTFE) grafts are next best, but are frequently complicated by graft "thrombosis," commonly caused not by hematologic abnormalities, but rather by intimal hyperplasia at the venous anastomosis. Unfortunately, the majority of patients have insufficient time to undergo pre-emptive creation of an arteriovenous fistula or graft, and most patients start hemodialysis with either a temporary or "semi-permanent" tunneled catheter, often placed in one of the internal jugular veins.

For patients who do undergo fistula creation, either in advance of (optimally) or after starting hemodialysis, a sizeable fraction of arteriovenous fistulae never mature sufficiently to be usable for hemodialysis. It is common for patients to undergo three or more attempts at fistula creation, extending the time during which they experience a heightened risk of infection and venous stenosis/thrombosis of the internal jugular veins or in some cases other complications including superior vena cava syndrome. Therapeutic agents that could facilitate maturation of arteriovenous fistulae could

vastly improve the health and well-being of patients on hemodialysis, and could well result in enhanced survival.

Preliminary Data

Numerous small studies have attempted to improve short- and longer-term function of arteriovenous fistulae and grafts with a variety of therapeutic agents, including warfarin, aspirin, fish oil, dipyridamole and several newer antiplatelet agents, including ticlopidine and more recently clopidogrel (3-7). In order to address the pressing need for improved outcomes, the National Institutes of Health (NIH) National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) assembled the "Dialysis Access Consortium" more than 10 years ago – a consortium of highly qualified investigators whose aim was to design two major clinical trials to address failure of arteriovenous fistulae and grafts, respectively (8). Dr. Chertow served on the Data Safety and Monitoring Board for both of the DAC trials.

The DAC investigators conducted a randomized, placebo-controlled trial of clopidogrel in patients receiving arteriovenous fistulae (9) (another trial examining arteriovenous grafts will not be discussed here). Interestingly, clopidogrel was shown to enhance short-term patency of arteriovenous fistulae, but failed to result in improved maturation, sufficient for the fistula to be consistently used for maintenance hemodialysis. Roughly six of 10 patients assigned to the trial (all at outstanding clinical centers) failed to have a usable fistula at 3-4 months, highlighting the need for more effective therapy. Despite the DAC fistula study having been stopped prematurely for "efficacy" (on the primary outcome of early fistula patency), few patients receive clopidogrel for this purpose in clinical practice.

Vorapaxar, Cardiovascular Disease and ESRD

PAR-1 receptors are expressed by platelets, endothelial cells and atheromatous plaques suggesting important roles in tissue response to injury, inflammation and thrombosis (10). Vorapaxar may have a role in preventing vascular access complications.

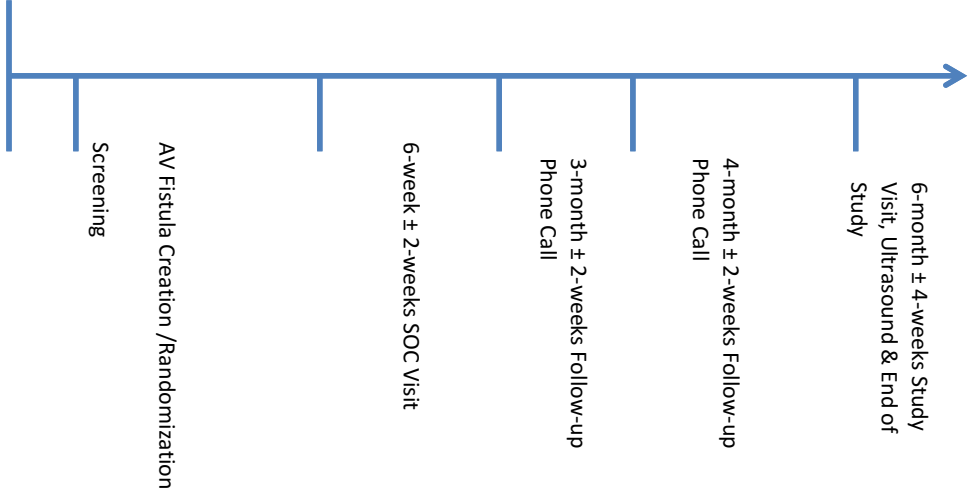
Vorapaxar has been studied in two large cardiovascular outcome trials – TRA-2P and TRACER (11, 12). In both trials, vorapaxar reduced the composite of CV death, MI and stroke with an excess in bleeding. Patients with renal dysfunction were not excluded. Vorapaxar has been approved by the FDA for secondary prevention in patients with stable cardiovascular disease. Recent analyses from TRACER showed non-heterogeneity of treatment effects on safety and efficacy outcomes in patients with and without renal dysfunction (Mahaffey KW, ESC abstract presentation). Additionally, Kosoglou et al. showed in a relatively small study that the pharmacokinetics of vorapaxar were not altered by ESRD, suggesting that dosing could proceed without modification in this population (13).

2.3 Study Design

This is a randomized placebo-controlled double-blind pilot trial. Study procedures will be conducted at Stanford University Medical Center, and Santa Clara Valley Medical Center (SCVMC). All standard-of-care (SOC) procedures will be conducted at the respective sites. However, the final 6-month study visit will be conducted at Stanford for all participants irrespective of whether they were enrolled at Stanford or SCVMC. We expect to enroll 50 patients. Patients will be assigned to treatment groups with a 1:1 randomization in blocks of 4 at the conclusion of the AV fistula creation. Patients will be stratified based on fistula location (lower arm versus upper arm).

Inclusion Criteria

1. Age >18
2. Receiving or planning to receive maintenance hemodialysis

	<ol style="list-style-type: none"> 3. Ability to sign informed consent 4. 3 mm venous diameter within recipient vein <p>Exclusion Criteria</p> <ol style="list-style-type: none"> 1. History of stroke, transient ischemic attack or intracranial hemorrhage 2. History of or high level of suspicion for, severe arterial insufficiency of the hand 3. Indication or ongoing therapy with other antiplatelet agents, other than aspirin 81 mg daily 4. Indication or ongoing therapy with anticoagulants, including warfarin, low molecular weight heparin, factor Xa inhibitors or direct thrombin and other inhibitors.
<p>2.4 Study Flowchart</p>	
<p>2.5 Study Procedures</p>	<p>Recruitment and Screening: Recruitment will be by invitation and referral from individuals' treating physicians at Stanford and SCVMC . Generally, initial screening will be performed at the time of consultation for dialysis access. Patients who appear to meet the study criteria and express interest in participation will be referred to the study team to be contacted for full screening.</p> <p>Consent: For eligible patients informed consent will be obtained prior to the day of surgery, generally by phone and mail or in person at the preoperative visit.</p> <p>Baseline demographics (preoperative visit, standard of care): The following data, which is collected as standard of care at the preoperative visit, will be utilized for baseline data with patient approval via the consent process:</p> <ul style="list-style-type: none"> • Age, sex, race, ethnicity, past medical history, medications, previous hemodialysis access surgery • Baseline blood pressure in each arm and vascular exam • Baseline vein measurements <p>Operative details (standard of care): The following data, which is collected during the AV Fistula Creation Procedure as standard of care, will be utilized for operative data with patient approval via the consent process:</p> <ul style="list-style-type: none"> • Location of anastomosis (lower or upper arm) • Vein used (cephalic or basilic) • Type of fistula (radiocephalic, brachiocephalic, brachio basilic, other)

2.5 Study Procedures

- Quality of artery (normal, moderate calcification, severe calcification)
- Palpable thrill through completion (yes or no)
- Audible bruit (yes or no)
- BARC Bleeding Classification
- GUSTO Bleeding Classification

Randomization: Randomization will be performed after successful creation of an arteriovenous fistula, on the day of surgery.

Treatments to be compared: Half of enrolled patients will receive the study drug (vorapaxar [Zontivity™] 2.5 mg daily) and half will receive a look-alike placebo.

Study drug: The study drug (12-week supply of study drug or placebo) will be dispensed to enrolled patients on the day of surgery. Participants will be instructed to start taking their study medications on Day-two post-surgery.

6-weeks Follow-up Clinic Visit + Ultrasound (standard of care)

Patients will return approximately 6 weeks after randomization to the site of their AV fistula creation procedure for a standard-of-care visit where the following data will be collected and provided to the study team:

- Patency of fistula (yes/no)
- Fistula being used for dialysis at least 6 times in 3 weeks (yes/no)
- Diameter of fistula by ultrasound
- Velocities of fistula by ultrasound
- Adverse events
- Additional procedures performed to aid in fistula maturation (yes/no)
 - Type of procedure
 - Successful (yes/no)
- BARC and Gusto Bleeding Classification

3-month Follow-up Phone Call (study visit):

Approximately 3 months after randomization patients will have a study phone call with a member of the research team where the following data will be collected:

- Patency of fistula (yes/no)
- Fistula being used for dialysis at least 6 times in 3 weeks (yes/no)
- Adverse events
- Additional procedures performed to aid in fistula maturation (yes/no)
 - Type of procedure
 - Successful (yes/no)
- BARC and Gusto Bleeding Classification

4-month Follow-up Phone Call (study visit):

Approximately 4 months after randomization patients will have a study phone call with a member of the research team where the following data will be collected:

- Patency of fistula (yes/no)
- Fistula being used for dialysis at least 6 times in 3 weeks (yes/no)
- Adverse events
- Additional procedures performed to aid in fistula maturation (yes/no)
 - Type of procedure
 - Successful (yes/no)
- BARC and Gusto Bleeding Classification

6-month Follow-up Clinic Visit + Ultrasound + End of Study (study visit):

Patients will have a final study visit at approximately 6 months, at Stanford University Medical Center Vascular Clinic where the following data will be collected:

- Patency of fistula (yes/no)
- Fistula being used for dialysis at least 6 times in 3 weeks (yes/no)

	<ul style="list-style-type: none"> • Diameter of fistula by ultrasound • Velocities of fistula by ultrasound • Adverse events • Additional procedures performed to aid in fistula maturation (yes/no) <ul style="list-style-type: none"> ○ Type of procedure ○ Successful (yes/no) • BARC and Gusto Bleeding Classification <p>Participation in this study will not affect standard care of patients with AV fistulae receiving hemodialysis. The only additional treatment is administration of the study drug or placebo and additional monitoring, including one additional ultrasound, for 6 months.</p> <p>Adverse events reporting process: The PI will review aggregated AEs each month, and AEs will be reported to the sponsor and the IRB per research guidelines. Participation for the individual will terminate if they have a serious adverse reaction that prevents future participation. In the event of adverse effects, their primary physician will be notified</p>
2.6 Study Duration	<p>We estimate 24 months will be required to recruit patients with an additional six months to complete follow-up of the last enrolled subject for a total of 30 months for recruitment and final assessments.</p>
2.7 Statistical Analysis and Sample Size Justification	<p>Data management and statistical coordination of the study will be performed by members of the Quantitative Sciences Unit (QSU) in the Department of Medicine at Stanford University School of Medicine and in the Data Coordinating Center in the Department of Medicine. The REDCap data managements system will be used to create the data platform for storage of the clinical information.</p> <p>Vascular Ultrasound studies will be performed at the site of surgery, either at Stanford University Hospital or SCVMC . Studies will be interpreted by the ordering vascular surgeon and reviewed by the Principal Investigator.</p> <p>Randomization codes will be generated in block size of 4 by a statistician in the QSU.</p> <p>Statistical analyses will be performed by MS level and PhD level statisticians in the QSU. Randomized treatment allocation will only be unblinded when all follow-up is complete, data have been cleaned and the trial statistician, Co-Investigators and Principal Investigator are in agreement.</p> <p><i>Variables/Time Points of Interest</i></p> <p><u>Primary Efficacy Outcome</u></p> <p>Time to AV fistula functional maturation (defined as successful cannulation of the AV fistula for six hemodialysis sessions within three weeks).</p> <p><u>Secondary Efficacy Outcomes</u></p> <p>AV fistula use within 180 days of surgery.</p> <p>AV fistula patency at 150-180 days, with at least 50% increase in vein diameter by ultrasound compared with preoperative vein diameter measurement.</p>

AV fistula functional or anatomic maturation at 180 days as determined by the PI

Safety Outcomes

Bleeding events (GUSTO and BARC Criteria)

BARC Bleeding Classification:

Type 0: No bleeding

Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2: Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3

Type 3a

Overt bleeding plus hemoglobin drop of 3 to 5 g/dL* (provided hemoglobin drop is related to bleed)
Any transfusion with overt bleeding

Type 3b

Overt bleeding plus hemoglobin drop >5 g/dL* (provided hemoglobin drop is related to bleed)
Cardiac tamponade
Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
Bleeding requiring intravenous vasoactive agents

Type 3c

Intracranial hemorrhage (does not include micro-bleeds or hemorrhagic transformation, does include intraspinal)
Subcategories confirmed by autopsy or imaging or lumbar puncture
Intraocular bleed compromising vision

GUSTO Bleeding Classification

Severe: Bleeding* that was fatal, intracranial, or that caused hemodynamic compromise requiring intervention (e.g., systolic blood pressure <90 mm Hg that required blood or fluid replacement, or vasopressor/inotropic support,** or surgical intervention).

Moderate: Bleeding* requiring transfusion of whole blood or packed red blood cells without hemodynamic compromise (as defined above).

Mild: Bleeding*: Bleeding without blood transfusion or hemodynamic compromise.

*In all cases, bleeding must be clinically overt.

	<p>**Need for vasopressor/inotropic support for hemodynamic compromise, even if blood pressure</p> <p>Statistical Methods:</p> <p>Descriptive statistics such as means, medians, standard deviations and interquartile ranges will be presented for continuous measurements, and frequency statistics will be presented for categorical characteristics. Graphical tools such as histograms and boxplots will be used to assess distributional aspects of continuous variables.</p> <p>Cumulative incidence plots will be derived to depict time to fistula use, stratified by treatment arm and fistula location.</p> <p>The primary outcome is time to AV fistula maturation, defined as successful cannulation of the AV fistula for six hemodialysis sessions within three weeks.</p> <p>Subjects who are lost to follow up or who die prior to maturation will be censored at the time of death or last recorded activity.</p> <p>Our primary analysis will be based on the intention-to-treat principle. To that end, patients will be analyzed according to their randomized treatment assignment, and all patients randomized to treatment assignment will be included in the analysis even if they are lost to follow up or die before the end of their observation period. We will use a log-rank test stratified by location of fistula to assess whether time to maturation of AV fistula differs between treatment arms (vorapaxar versus placebo). The test will be two-sided and conducted at the 0.05 level of significance.</p> <p>A Cox proportional hazards regression model of treatment arm and other covariates of interest will be employed secondarily to estimate an adjusted treatment effect.</p> <p>Other secondary analyses involve the use of logistic regression techniques to evaluate the effect of treatment on secondary endpoints – use of AV fistula within 180 days and AV fistula patency within 150-180 days.</p> <p>Power/Sample Size:</p> <p>We have sufficient power to address our primary aim. Based upon a sample size of n=25 patients per group for this pilot study, we have approximately 70% power to detect a hazard ratio of 2.05 between treatment arms, assuming that only 50% of subjects will experience maturation by six months post randomization in the placebo group. If only 40% of subjects experience maturation by six months post randomization we have over 70% power to detect a hazard ratio of 2.15.</p>
<p>2.8 Specific Drug Supply Requirements</p>	<p>Merck will provide the study drug and matching placebo in study kits. At conclusion of the study or upon drug expiration, the Merck GRS will be responsible for issuing a Drug Disposition Letter to the investigator for US based studies. The study investigators will be responsible for the destruction of the supplies at the study center pursuant to the ICH/GCP Guidelines, local regulations and the investigator's institutional policies. The study investigators will responsible for keeping accurate records of the clinical supplies, the amount dispensed to and returned by the patients, and the disposition at the end of the study.</p>

2.9 Adverse Experience Reporting	<p>A Data Safety Monitoring Board (DSMB) comprised of one vascular surgeon, one physician with expertise about vorapaxar and one experienced in clinical trials will review unblinded data after 10 patients have completed follow-up 6-month ultrasound and after 30 patients have completed follow-up 6-month ultrasound evaluation.</p> <p>Model study agreement will be used for reporting of adverse events.</p>
2.10 Itemized Study Budget	<p>See attached.</p>
2.11 References	<ol style="list-style-type: none"> 1. United States Renal Data System 2013 Annual Report, Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases. 2. Brescia MJ, Cimino JE, Appel K, Hurwich BJ. Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula. N Engl J Med 1966; 275:1089. 3. Andrassy K, Malluche H, Bornefeld H, et al. Prevention of clotting of AV cimino fistulae with acetylsalicyl acid: results of a prospective double blind study. Klin Wochenschr 1974;52:348. 4. Crowther MS, Clase CM, Margetts PJ. Low-intensity warfarin is ineffective for the prevention of PTFE graft failure in patients on hemodialysis: a randomized controlled trial. J Am Soc Nephrol 2002; 2002; 13:2331. 5. Fiskerstrand CE, Thompson IW, Burnet ME, Williams P, Anderton JL. Double-blind randomized trial of the effect of ticlopidine in arteriovenous fistulas for hemodialysis. Artif Organs. 1985; 9:61. 6. Osborn G, Escofet X, DaSilva A. Medical adjuvant treatment to increase patency of arteriovenous fistulae and grafts. Cochrane Database Syst Rev 2008; 4:CD002786. 7. Kaufman JS. Antithrombotic agents and the prevention of access thrombosis. Semin Dial. 2000; 13:40. 8. Dember LM, Kaufman JS, Beck GJ, et al. Design of the Dialysis Access Consortium (DAC) clopidogrel prevention of early AV fistula thrombosis trial. Clin Trials. 2005; 2:413. 9. Dember LM, Beck GJ, Allon M, et al. Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis: a randomized controlled trial. JAMA 2008; 299:2164. 10. Hirano K. The roles of proteinase-activated receptors in vascular physiology and pathophysiology. Arterioscler Thromb Vasc Biol 2007; 27: 27. 11. Morrow DA, Braunwald E, Bonaca MP et al. Vorapaxar in the secondary prevention of atherothrombotic events. N Engl J Med 2012;366:1404. 12. Tricoci P, Huang Z, Held C, et al. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. N Engl J Med 2012; 366:20. 13. Kosoglou T, Kraft WK, Kumar B, et al. Pharmacokinetics and pharmacodynamics of the novel PAR-1 antagonist vorapaxar in patients with end-stage renal disease. Eur J Clin Pharmacol 2012; 68:1049.
2.12 Publication Plan	<p>We will publish at least one manuscript describing clinical trial design and results. Our projected target date for publication is six months after closing the trial. We plan to submit the study to the Journal of Vascular Surgery or Clinical Journal of the American Society of Nephrology. We anticipate two abstracts: one each for annual meetings of the Society of Vascular Surgery and American Society of Nephrology</p>
	<p>See attached.</p>

2.13 Curriculum Vitae	
2.13 Protocol Submission for Investigator-Initiated Studies	<p>U.S. protocols should be submitted by US investigators directly or through the Global Research Specialist at www.merckiiisp.com</p> <p>Non U.S. protocols should be submitted to the MSD office by the investigators.</p>