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

Statistical Analysis Plan

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Table of Contents

AMENDMENT HISTORY

November 3, 2016:	**Final version of SAP. Version 1.0**
May 16, 2018:	**Vorapaccess SAP revised. Version 2.0** **Added a new secondary outcome** **Added a sentence on the deviation from the planned analysis due to low enrollment and early stopping of trial.**
June 11, 2018:	**Updated the definition of the secondary outcome "'AV fistula functional or anatomic maturation at 180 days as determined by the PI"**

1. Introduction

1.1. 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 matures 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.

1.2. 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.

1.3. 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. Study Design

2.1. Study Design

This is a randomized placebo-controlled double-blind pilot trial. Half of enrolled patients will receive the study drug (vorapaxar [Zontivity™] 2.5 mg daily) and half will receive a look-alike placebo.

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). Randomization will be performed after successful creation of an arteriovenous fistula, on the day of surgery. We expect to randomize 50 patients.

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.

2.2. Study Participants

Patients meeting inclusion and exclusion criteria at Stanford University Medical Center or Santa Clara Valley Medical Center (SCVMC) will be eligible to participate in the study. Study procedures will be conducted at Stanford University Medical Center and 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.

Inclusion Criteria

1. Age >=18 years
2. Receiving or planning to receive maintenance hemodialysis
3. Candidate for arteriovenous fistula
4. Ability to sign informed consent

5. At least 3 mm venous diameter within recipient vein

Exclusion Criteria

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
5. Indication or ongoing therapy with strong inhibitors or strong inducers of CYP3A

Study participants will be followed up at approximately 6 weeks, 3 months, 4 months and 6 months after randomization. At each of these visits, data will be collected on the following measures:

- 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

In addition, at the 6 week and 6 month follow up visits, data will be collected on:

- Diameter of fistula by ultrasound
- Velocity of fistula by ultrasound

2.3. Study Endpoints

The primary efficacy outcome is time to AV fistula functional maturation (defined as successful cannulation of the AV fistula for six hemodialysis sessions within three weeks).

The secondary efficacy outcomes are:

- AV fistula use within 180 days of surgery
- AV fistula patency at 150-180 days, with at least 50% increase in vein diameter by ultrasound compared with preoperative vein diameter measurement
- Update: New secondary outcome added: AV fistula functional or anatomic maturation at 180 days as determined by the PI

The safety outcomes are bleeding events as determined by BARC and GUSTO 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

- Type 4 CABG bleeding
- Type 5: Fatal bleeding

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.
**Need for vasopressor/inotropic support for hemodynamic compromise, even if blood pressure

3. Statistical Analysis

3.1. Data monitoring and quality

We will perform periodic data quality checks for missing data using reports generated in REDCap where data are being collected. After 4 patients have completed follow-up we will review the data for completeness and value checks. Thereafter, we will conduct two additional data quality checks: after an additional 10 and 30 patients have completed follow-up.
Ongoing data monitoring will be conducted by the monitoring coordinator at SCCR to ensure compliance.

3.2. Handling of Missing Data

We anticipate minimal missing data in this study. We expect that a small proportion of subjects randomized for the study (1-2 subjects) will not complete all visits. We will fully describe missing data for each variable and any pertinent patterns of missingness (e.g. how missingness is related to specific baseline measurements or time, if at all). The statistical methods we will use are particularly flexible for missing data and allow for systematic missingness that is related to observed features.

3.3. Descriptive Statistics

We will provide descriptive statistics such as means, medians, standard deviations and interquartile ranges for continuous measurements, and frequency statistics for categorical characteristics. We will use graphical tools such as histograms and boxplots to assess distributional aspects of continuous variables.

3.4. Statistical Analysis:

We will derive cumulative incidence plots to depict time to fistula use, stratified by treatment arm and fistula location.

The primary outcome is time to AV fistula maturation, defined as successful cannulation of the AV fistula for six hemodialysis sessions within three weeks.

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.

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.

A Cox proportional hazards regression model of treatment arm and other characteristics of interest (if required) will be employed secondarily to estimate an adjusted treatment effect.

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, AV fistula patency within 150-180 days and AV fistula functional or anatomic maturation at 180 days as determined by the PI. We will also compare rates of bleeding by treatment arm using t-tests or Wilcoxon rank sum tests as appropriate.

UPDATED: Based on low enrollment and early termination of the study, the planned analysis as described above will not be conducted. Instead, we will conduct a descriptive analysis only.

UPDATED: The secondary outcome "AV fistula functional or anatomic maturation at 180 days as determined by the PI" will be defined using clinically adjudicated after a review of the medical record.

Power/Sample Size

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.

4. Statistical conventions

This section details general conventions to be used for the statistical analyses and presentation of the data. Departures from these general conventions may be given in the specific detailed sections of this analysis plan.

1. SAS Version 9 or R Version 3 will be the statistical software package used for all data analyses.
2. Continuous variables will be presented with mean, standard deviation, median (25th percentile, 75th percentile), minimum and maximum values. Categorical variables will be presented as number of subjects and percentage of number of subjects by levels of the variable.
3. The number and percentage of responses will be presented in the form XX (XX) where the percentage is in the parentheses. Unless otherwise specified, the denominator for percentages will be the number of subjects in a given treatment group within the analysis population of interest. The denominator will be included when it differs from the standard analysis population.

4. All summary tables will include the analysis population sample size (i.e., number of subjects).
5. Change from baseline will be calculated for each period as follows:
   Change from baseline = Post-baseline value – baseline value.
6. Date variables will be formatted as DD-MON-YYYY for presentation. In the case of missing day, month, and/or year information, "NA" will be presented. For example, a date with a missing month and day will be presented as NANAYYYY.
7. Unless otherwise stated, statistical comparisons will be performed using two-sided significance tests. An alpha level of 0.05 will determine significance unless otherwise noted for a specified analysis.
8. When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts.
9. Unless specified otherwise, data will be presented by treatment and control subjects.

5. Adverse events data and reporting process

Adverse events data will be collected at each follow up visit as described above in the section on Study Participants.

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 he/she has a serious adverse reaction that prevents future participation. In the event of adverse effects, the patient's primary physician will be notified.

References

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.

Appendix 1: Tables and figures

Table 1. Demographic characteristics of study population

Characteristics	**Treatment**		**Control**	
	Left arm N (%)	**Right arm N (%)**	**Left arm N (%)**	**Right arm N (%)**
Age (years) Mean (SD) Median (IQR)				
Site Stanford University Santa Clara Valley				
Male				
Race White Black Asian American Indian Pacific Islander Other Unknown				
Ethnicity Hispanic Non-Hispanic Unknown				
BMI Mean (SD) Median (IQR)				

Table 2. Baseline clinical characteristics of study population

Characteristics	**Treatment**		**Control**	
	Left arm N (%)	**Right arm N (%)**	**Left arm N (%)**	**Right arm N (%)**
Had previous surgery Ipsilateral tunnel catheter access Permanent ipsilateral AV fistula access Permanent ipsilateral AV graft access Contralateral tunnel catheter access Permanent contralateral AV fistula access Permanent contralateral AV graft access Other surgery type				
Medical history None Routinely hypotensive Diabetes Coronary artery disease COPD Congestive heart failure Peripheral artery disease Stroke Intracranial hemorrhage Hypertension Cancer Peptic ulcer disease Other				
Concomitant Medications None Daily aspirin Statins Insulin Oral diabetic medications Antifungal agents ACE inhibitors ARBs Beta blockers Calcium channel blockers Other antihypertensive Diuretics Antiarrhythmics Other medications				

Table 3. Efficacy and safety outcomes

	Treatment		**Control**		**Hazard ratio (95% CI)**
	Left arm N (%)	**Right arm N (%)**	**Left arm N (%)**	**Right arm N (%)**	
Efficacy outcomes					
Time to fistula maturation (days) Mean (SD) Median (IQR)					
AV fistula use within 180 days of surgery					
AV fistula patency at 150-180 days, with at least 50% increase in vein diameter by ultrasound compared with preoperative vein diameter measurement					
Safety outcomes					**Odds ratio (95% CI)**
BARC bleeding Type 0 Type 1 Type 2 Type 3a Type 3b Type 3c Type 4 Type 5					
GUSTO bleeding Mild Moderate Severe					

Table 4. Adverse events and other outcomes

	Treatment		**Control**		**Odds ratio (95% CI)**
	Left arm N (%)	**Right arm N (%)**	**Left arm N (%)**	**Right arm N (%)**	
Serious adverse events					
Unexpected adverse events					
Other adverse events None Anemia Depression Rash Iron deficiency Retinopathy Retinal disorder Diplopia/oculomotor disturbances Other					
Other outcomes Hospitalization Unstable angina Myocardial infarction Cardiac catheterization PCI CABG Non-coronary vascularization Stroke TIA Transfusion					

Figure 1. Kaplan-Meier plot of time to fistula maturation by treatment arm and location of fistula

Figure 2. All outcomes with forest plot for point estimate and 95% confidence interval