Study Protocol Cover Page

Protocol Title:
Prospective, Randomized Trial Comparing Recombinant von Willebrand Factor (rVWF) Plus Tranexamic Acid (TA) vs. rVWF Alone to Reduce Postpartum Hemorrhage in Women with von Willebrand Disease: *The VWD-Woman Trial*

Short Title: The VWD-Woman Trial
Protocol Number: PRO20030186
ClinicalTrials.gov Identifier (NCT Number): NCT04344860
Version Number / Date: Version 3.2 – 13 June 2023

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Sponsor / Funding Source: Takeda Pharmaceuticals USA

Study Phase: Phase III Pilot Trial
Study Design: Single-center, prospective, randomized, open-label trial

Statistical Analysis Plan:
The Statistical Analysis Plan (SAP) is included within this protocol (Section 3.3). No standalone SAP is submitted.

Confidentiality Statement:
This document contains confidential information and is intended solely for submission to regulatory authorities, investigators, and authorized study personnel. It must not be disclosed to any other parties without prior written authorization from the Principal Investigator and/or Sponsor.

Prospective, Randomized Trial Comparing Recombinant von Willebrand Factor (rVWF) Plus Tranexamic Acid (TA) vs. rVWF Alone to Reduce Postpartum Hemorrhage in Women with von Willebrand Disease: The VWD-Woman Trial

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Principal Investigator: Nicoletta Machin, DO

Funded by: Takeda

Version Number: v3.2

13 June 2023

PROTOCOL SUMMARY

Title: **The Von Willebrand WOMAN (VWD-Woman) Trial:** A Phase III Randomized, Pilot Trial Comparing Recombinant von Willebrand Factor (rVWF, Vonvendi®) plus Tranexamic Acid (TA, Cyclokapron®) vs. rVWF, *Vonvendi®* alone to Prevent

Postpartum Hemorrhage in Women with Von Willebrand Disease

Study Description: This is a prospective, randomized single-center phase III pilot clinical trial comparing recombinant von Willebrand factor (rVWF, Vonvendi®) plus tranexamic acid (TA, Cyclokapron®) vs. rVWF alone to reduce postpartum hemorrhage (PPH) in women with von Willebrand disease (VWD). We *hypothesize* that intravenous rVWF given just before delivery plus intravenous tranexamic acid within 3 hours of delivery is superior to rVWF alone in reducing postpartum blood loss.

Objective: The **Primary Objective** is to determine the efficacy of rVWF plus TA vs. rVWF alone in reducing postpartum hemorrhage in women with VWD.
The **Secondary Objectives** are to evaluate safety, tolerability, and mechanism of rVWF plus TA vs. rVWF alone in reducing PPH in women with VWD.

Endpoints: The **Primary Endpoint** is quantitative blood loss (QBL) calculated by a labor suite nurse at delivery. The **Secondary Endpoints** include safety assessment by lochial blood loss by pictorial blood assessment chart (PBAC), blood products, transfusion, and hysterectomy within 21 days of delivery; and mechanism of PPH reduction by VWF assays, fibrinogen, and d-dimer.

Study Population: Study subjects will be females age $\geq$ 18 years of age with von Willebrand disease, defined by VWF:RCo <0.50 IU/dL (historic) and previous bleeding history, undergoing vaginal or caesarean section delivery. A total of 20 eligible subjects with VWD will be enrolled in this 2-year trial.

Site Enrolling Subjects: Pilot: Participating site is HCWP, and Magee Hospital obstetricians.

Description of Study Intervention: There are two study interventions: rVWF plus tranexamic acid vs. rVWF alone.
Recombinant von Willebrand factor (rVWF, Vonvendi®) is an FDA-approved clotting factor approved for treatment or prevention of bleeds including postpartum hemorrhage hemorrhage in VWD. It is an intravenous agent administered in single-use vials containing approximately 650-1300 IU per vial as a sterile, lyophilized powder. The vials are reconstituted with 5-10 ml vial of sterile water for injection, USP, which is transferred by two-way needle into the lyophilized powder for reconstitution, and the reconstituted vial infused over 5-10 minutes, at 80 IU/kg (per pre-pregnancy weight) at delivery (or epidural), and days 1 and 2 postpartum.
Tranexamic acid (TA, Cyclokapron®) is an FDA-approved anti-fibrinolytic agent for the treatment or prevention of bleeding in bleeding disorders. It is an intravenous agent supplied as a sterile, unpreserved, colorless solution administered in single-dose polymeric bags containing 1000 mg tranexamic acid in sodium chloride in 100 ml and given at a rate of 1 ml/ minute, at 1 g within 3 hours after delivery.

Trial Arms	
Arm A	rVWF 80 IU/kg at delivery (or epidural), and day 1, 2 plus TA 1 gm IV within 3 hours after delivery
Arm B	rVWF 80 IU/kg at delivery (or epidural) and day 1, 2 alone

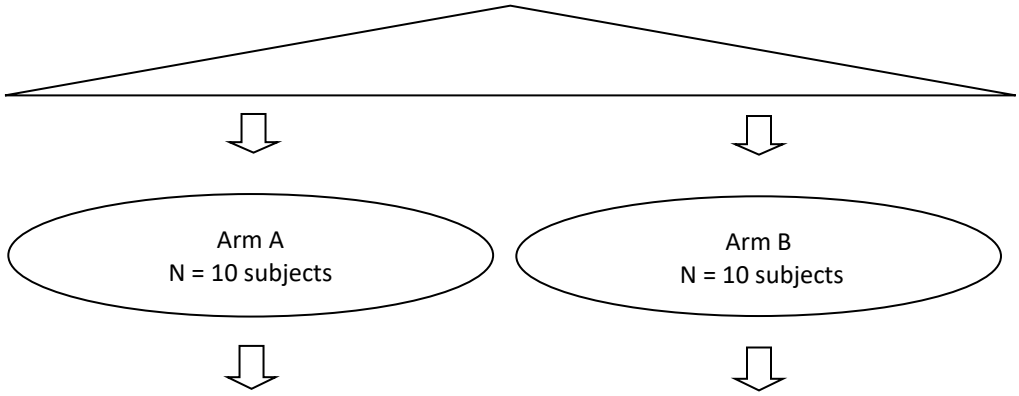
Study Duration: This is a 8-week inpatient trial in which all subjects will be randomized to one of two treatment arms and followed for 4 weeks.

PROTOCOL SCHEMA

Screening
Week -4
Visit 1

Subjects will be screened at 32-39 weeks' gestation, after signed, informed consent, by inclusion and exclusion criteria; undergo a history, vital signs, and baseline labs: hemoglobin, hematocrit, platelets, Fe, TIBC, ferritin, VWF assays (VWF:RCoF, VWF;Ag, FVIII:C), fibrinogen, and d-dimer, and be randomized to one of two treatment arms.

Admission
Childbirth
Week 0
Visit 2



Week 0
Day 0-2
Visits 3-4

On admission for childbirth, subjects will have baseline blood counts, VWF assays, and d-dimer drawn and receive the initial study intervention at delivery (or epidural), and on days 1 and 2 postpartum. At 1 day and 2 days postpartum, lochial blood loss by PBAC, blood products, transfusion, and concomitant medications will be reviewed; and blood counts, VWF assays, fibrinogen, and d-dimer will be drawn.

Week 3
Visit 5

Final Assessment
Subjects will return to clinic 21 days postpartum (Visit 5), lochial blood loss by PBAC, blood products, transfusion, and medications will be reviewed; and blood counts, VWF assays, fibrinogen, and d-dimer will be drawn.

ABSTRACT

This is a single-center randomized phase III pilot clinical trial, the **VWD-Woman Trial**, in which 20 pregnant women with von Willebrand disease, defined as VWF:RCo <0.50 IU/ml (historic) and previous bleeding history, are enrolled. Subjects will include women with VWD age 18 years of age and older, excluding those who have a bleeding disorder other than VWD. Once enrolled, subjects who meet all of the inclusion and none of the exclusion criteria will be randomized to recombinant Von Willebrand factor (Vonvendi, rVWF®) with Tranexamic Acid (TA, cyclokapron®) or recombinant Von Willebrand factor (Vonvendi, rVWF®) alone to prevent postpartum hemorrhage after a vaginal or caesarean section. The primary endpoint is quantitative blood loss (QBL) collected by a labor suite nurse at delivery, and secondary endpoints include safety assessment for postpartum lochial blood loss by Pictorial Blood Assessment Chart (PBAC), transfusion, blood products, thromboembolic events, and hysterectomy within 21 days; and mechanism of PPH reduction by VWF assays (VWF:RCo, VWF:Ag, VIII:C), fibrinogen, and d-dimer. Blood draws are at 5 time points, including at 32-39 weeks' gestation (screening), on admission for childbirth, and at 1 day, 2 days, and 21 days after delivery. The VWD-Woman Trial is considered greater than minimal risk as study drugs are given at delivery and special coagulation studies are obtained.

Principal Investigator: Nicoletta Machin, DO
Co-Investigators: Maria Brooks, PhD

Protocol Title: The Von Willebrand WOMAN (VWD-Woman) Trial: A Phase III Randomized, Pilot Trial Comparing Recombinant von Willebrand Factor (rVWF, Vonvendi®) plus Tranexamic Acid (TA, Cyclokapron®) vs. rVWF, *Vonvendi*® alone to Prevent Postpartum Hemorrhage in Women with Von Willebrand Disease

1.0 Objective and Specific Aims

The purpose of this 8-week single center, randomized, open-label pilot phase III trial is to prevent postpartum hemorrhage in women with von Willebrand disease. This 8-week open-label, randomized, controlled single-center trial will compare recombinant von Willebrand factor (rVWF, Vonvendi®) plus Tranexamic Acid (TA Cyclokapron®) vs. rVWF, *Vonvendi*® alone to reduce postpartum hemorrhage (PPH) in women with VWD. Both drugs are approved by the FDA to prevent and treat bleeding in individuals with von Willebrand disease. In this trial, subjects will be pregnant women age 18 years and older with VWD, defined as VWF:RCo <0.50 IU/dL and past bleeding history. The research is considered greater than minimal risk as it Involves study drugs at delivery, and special coagulation studies are obtained. Blood loss at delivery will be by quantitative blood loss (QBL) at delivery calculated by a labor suite nurse, and postpartum blood loss will be lochial blood loss by pictorial blood assessment chart (PBAC), validated for postpartum blood loss. The primary endpoint is quantitative blood loss (QBL) during C-section and vaginal delivery and calculated by a labor suite nurse. The secondary endpoints will include i) assessment of safety by lochial blood loss by pictorial blood assessment chart (PBAC) validated for postpartum blood loss, transfusion, blood products, thromboembolic events, and hysterectomy within 21 days of delivery; and ii) assessment of the mechanism of PPH reduction by von Willebrand assays (VWF:RCo, VWF:Ag, FVIII:C), coagulation assays (fibrinogen, and d-dimer measured at screening (32-39 weeks') gestation (screening), on admission for childbirth, and at 1, 2, and 21 days postpartum. The trial will assess PPH hemorrhage reduction after each subject completes the 8-week trial.

2.0 Background and Significance

2.1 Significance

Von Willebrand disease (VWD) is the most common congenital bleeding disorder, occurring in 1% of the population.[1] It is caused by quantitative or qualitative deficiency of von Willebrand factor (VWF). VWF is a multimeric plasma glycoprotein which serves both as a carrier molecule for factor VIII and as an adherent protein that mediates platelet adhesion to damaged vascular endothelium.[2,3] The bleeding in VWD is primarily mucosal, including bruising, epistaxis, menorrhagia, and postoperative bleeding, and, in women of child-bearing years, reproductive tract bleeding, including postpartum hemorrhage (PPH).[3,4] Women with VWD have a 1.5-fold greater odds of PPH than controls,[5] with an incidence of 5.5%.[6] Over one-quarter of women with VWD and PPH are anemic, or twice as many as non-VWD women with PPH, and are more likely to require a red blood cell transfusion.[6] When severe, < 7 g/dL, anemia is refractory to routine iron supplementation and associated with a 2-fold greater odds for maternal death.[7] These data suggest PPH is a significant cause of maternal morbidity and mortality.

Postpartum hemorrhage is the leading cause of maternal death in the world and accounts for one third of maternal deaths in the United States. Defined as blood loss exceeding 1000 mL in first 24 hours with vaginal delivery or cesarean delivery,[8] PPH peaks in the first 2-3 hours postpartum, a time during which there is early activation of the fibrinolytic system, with a 2-fold increase in TPA (tissue plasminogen activator).[9] Overall, while uterine atony is the major cause of PPH, accounting for 63% of PPH cases,[10] and uterotonic agents are effective in reducing PPH,[10] but in 37% they may fail.

Current guidelines indicate that management of postpartum hemorrhage should include hemostatic agents, including antifibrinolytic agents, e.g. tranexamic acid, which is an inhibitor of plasmin-mediated

fibrinogen and fibrin breakdown, along with transfusion support including blood and plasma products.[10] Tranexamic acid (TA) has been shown not only to reduce blood loss after elective surgery[11] but also to reduce blood loss and mortality after trauma (CRASH-2).[12] In the WOMAN trial of over 20,000 women with postpartum hemorrhage, there was a significant reduction in bleeding and mortality from bleeding, when tranexamic acid (TA, Cyclokapron) was given at a dose of 1 gm IV within three hours of delivery.[13] This benefit was associated with a reduction in d-dimer,[14] and no adverse effects, in particular, no thrombotic complications.[13] Moreover, subsequent studies, including a meta-analysis of 25 trials showed that when TA was given preventively before vaginal and cesarean delivery, it reduced the rate of PPH, with no thrombosis.[15-17] No randomized trial has evaluated tranexamic acid when given within 3 hours of delivery in preventing PPH in women with VWD. Clearly, future trials are needed to determine the role of TA in preventing PPH in VWD.

In women with VWD, hemostatic support with clotting factor is the current approach to PPH prevention. Based on expert U.S., NHF and European guidance, a VWF level > 0.50 IU/dL is recommended before epidural delivery. [10,19-27] While some advocate a dose of VWF 50 IU/kg at delivery,[10, 19-21] there is no specific guidance regarding the optimal dose or duration to prevent PPH, although some advocate avoiding DDAVP which may be associated with hyponatremia due to fluid loss and replacement at delivery.[19] Yet, a dose of 50 IU/kg is lower than that recommended for other surgical procedures, 80 IU/kg,[19-21] attributed, in part, to fear of increasing the risk of thrombosis in the postpartum period. Yet, thrombosis is uncommon with VWF concentrate. In published studies, trials, and clinical experience over the last two decades, thrombosis occurs in less than 0.4%, even when doses as high as 100-200 IU/kg are given.[36] Yet, up to one-third of women with VWD develop PPH despite factor replacement.[22] In a prospective observational study, of women with VWD, even when VWF concentrate was given before and after delivery, VWF levels were lower and blood loss was greater in women with VWD than in controls,[23] and VWF levels peaked earlier than controls, at 4 hours postpartum, rapidly declined, and remained lower than controls for 3 weeks.[23] A more recent observational study found, however, no difference in PPH between those receiving 50 IU/kg and 80 IU/kg, the standard dose for surgery.[27] Finally, although it is known that third trimester VWF levels are inversely related to PPH risk,[22] and lower pre-pregnancy VWF and higher pre-pregnancy and third-trimester body weight are associated with PPH,[24] there are no established predictors of PPH. While the optimal VWF level and duration of treatment are not known, it is clear that 50 IU/kg is insufficient to prevent PPH.

Why there is increased blood loss and lower VWF levels at delivery in women with VWD, despite VWF treatment, remains unknown. The current recommended VWF dosing, 50 IU/kg, does not take into account the 1.5-fold increase in blood volume.[28] Yet, while not used in pregnant women with VWD, volume-based dosing, rather than weight-based factor dosing is routinely used in children and obese adults with hemophilia.[29] Yet, during pregnancy, the physiologic increases in cardiac output, extracellular fluid, renal blood flow, and glomerular filtration rate accelerate drug clearance,[30,31] and is the basis for blood volume-based dosing for a number of drugs in pregnancy.[32] Finally, the physiologic fibrinolysis that occurs in the first three hours postpartum may contribute to greater bleeding in the woman with a bleeding disorder such as VWD.

Therefore, we *hypothesize* that rVWF 80 IU/kg IV, a dose safe and effective in treatment and prevention of VWD bleeding, standardly administered for surgery, and appropriate for the 1.5-fold increase in blood volume in pregnancy, when given before and on day 1 and day 2 after delivery, *plus* tranexamic acid 1 gm IV, a dose safe and effective in treatment and prevention of postpartum hemorrhage and mortality related to PPH, will be superior to rVWF alone in reducing PPH in women with VWD. This trial will help to enhance our understanding of the coagulopathy and mechanism PPH in VWD and, will be consistent with the goals and objectives of Healthy People 2020, to develop safer, more effective products for treatment of VWD.

2.2 Significance. By studying the safety and biologic effects of rVWF with TA vs. rVWF alone, we hope to

determine in this pilot study the feasibility of the VWD-Woman trial, the purpose of which is to reduce postpartum hemorrhage in women with VWD. Specifically, if we demonstrate the clinical hemostasis, and safety and tolerability of VWD with or without TA, in reducing PPH women with VWD, this would provide evidence that our clinical trial is feasible and biologically plausible. Finally, the findings of this study will potentially provide new information to determine feasibility for use in a future prospective phase III randomized clinical trial to prevent postpartum hemorrhage in women with von Willebrand disease, and promote blood product safety, consistent with the goals of Healthy People 2020.

3.0 Research Design and Methods

3.1 Drug/Device Information

Recombinant VWF (rVWF, Vonvendi®) is an FDA-approved recombinant von Willebrand factor indicated for the treatment and prevention of bleeding episodes in individuals with von Willebrand disease. approved by the FDA for treatment or prevention of bleeds in VWD. rVWF is produced by DNA technology. It is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line that co-expresses both VWF and FVIII genes.[10] It is manufactured and formulated in the absence of animal or other human plasma proteins, thus eliminating the theoretical the risk of transmissible agents and other blood-borne pathogens. It contains ultra-large and high molecular weight multimers (HMWM) of VWF that are essential for platelet plug formation.[1,2] with no exposure to ADAMTS13 during the production process and thus contains intact HMWM and ULM.[10] rVWF has been shown to be safe and hemostatically effective in types 1, 2, and 3 VWD for treatment of bleeds, with 96.9% rating bleed control excellent or good, and was well tolerated, with no associated with any cardiac symptoms, and there were no thrombotic or severe allergic events, or antibodies to VWF or FVIII.[11,12] rVWF for injection is formulated as a sterile, non-pyrogenic lyophilized white to off-white powder for intravenous injection after reconstitution. The product contains tri-sodium citrate-dihydrate, 15 nM, glycine 15 mM, mannitol 20 g/L, trehalose-dihydrate, 10 g/L, and polysorbate 80, 0.1 g/L. It is available in single-dose vials for reconstitution containing nominal 650 or 1300 international units VWF:RCo. After reconstitution of the lyophilized powder and filtration/withdrawal into a syringe, all dosage strengths yield a clear, colorless solution free of particles. The 650 IU/vial is reconstituted with a 5-ml vial of sterile water for injection, USP; the 1300 IU/vial is reconstituted with a 10-ml vial of sterile water for injection. The resulting solutions for the individual 650 IU/vial and 1300 IU/vial have a pH of 7.3. A two-way needle will allow transfer of the diluent into the lyophilized powder for reconstitution and slow infusion over 5-10 minutes. Storage of rVWF post-reconstitution should be at room temperature not to exceed 25˚C (77˚F) for up to 3 hours.

Tranexamic acid (TA, Cyclokapron®) is an FDA-approved antifibrinolytic agent indicated for the treatment ofbleeding in individuals with fibrinolysis and has been used for years with a long safety profile in subjects with bleeding disorders. Tranexamic acid in sodium chloride is supplied for injection as a sterile, unpreserved, colorless solution in a single-dose polymeric bag containing 1,000 mg of tranexamic acid in 100 mL (10 mg/mL), sealed with a twist off port and oversealed in an aluminum pouch. It is infused at 1 mL per minute, or over 10 minutes. It is stored at 20˚C to 25˚C (68˚F -77˚F).

Once a subject is consented and identified as eligible for this trial, a unique subject number will be assigned to each subject by the GSPH Data Center, Pittsburgh PA. Study drug dosing will be given by Magee Women's Hospital research staff. Both drugs will be provided, by Takeda funding, through the Magee pharmacy per randomization code to subjects participating in this study. Once a subject is identified as eligible for the study, she will be assigned a unique ID number and randomized by the GSPH Data Center. The randomization code will be linked to study drug, rVWF and TA, and the accession number placed on the drug vial or bag, in agreement with the accession number assigned to each study subject. Each study drug will be labeled with storage, lot number, stability, production and expiration dates by the Magee Inpatient Research Pharmacy.

3.2 Research Design and Methods

This is an 8-week, randomized, open-label trial to evaluate the hemostatic efficacy of rVWF plus TA vs. rVWF alone to prevent postpartum hemorrhage, measured by quantitative blood loss (QBL) at delivery in women with VWD. We hypothesize that while rVWF is a hemostatic agent indicated for prevention and treatment of bleeding, including surgical bleeding and delivery, the physiologic fibrinolysis that occurs within three hours of delivery may contribute to an enhanced bleeding tendency in women with VWD and to their greater risk of PPH. We therefore propose to use tranexamic acid, an antifibrinolytic agent, together with rVWF to determine if the combination reduces PPH. It is anticipated that 20 subjects who meet eligibility criteria will enroll in and complete this study. All aspects of this study, including the rVWF infusion, screening, biologic effects study by von Willebrand tests (VWD profile), are considered experimental. This pilot study is an inpatient and outpatient study and will last up to 2 years. The duration of the study for each subject will be up to 8 weeks. With the exception of the screening visit (32-39 weeks' gestation) and the final visit (day 21 postpartum) at either the Hemophilia Center of Western PA (HCWP) or Magee Outpatient Clinic, the study will be performed while the subject is an inpatient at Magee Women's Hospital.

Based on the established safety and efficacy of rVWF in individuals with VWD including pregnant women and at childbirth,[34,35] and very low rate of thrombosis, 0.4%, based on 570 patients in 13 studies.[36] and the established safety and efficacy of TA in surgery,[11] trauma,[12] and childbirth,[13] it is anticipated that the proposed doses will be safe and well-tolerated, with no thrombosis, allergic reaction, or adverse effects.

The goal of the current study will be to obtain preliminary information on the safety and efficacy of rVWF given at 80 IU/kg at delivery and day 1, day 2, with or without TA 1 gm IV within 3 hours of delivery in reducing postpartum hemorrhage in 20 pregnant VWD subjects. If the study recruitment, randomization, drug administration, data collection and management are feasible, then the large, multicenter phase III trial will be initiated. As both drugs are FDA-approved and have been previously used in VWD patients without adverse effects, we anticipate none during the study. If any subject experiences any grade 3 or higher treatment-related toxicity, blood loss, allergic reaction (fever, chills, hives, tachycardia, chest discomfort), or thrombosis, the decision to continue the study will be made by a local Data Safety Monitoring Committee.

DOSING SCHEMA

Study Arms	No. Subjects	Study Drug(s) at Delivery	Study Drug Postpartum
Arm A	10	rVWF 80 IU/kg + TA 1 gm	rVWF 80 IU/kg days 1 and 2
Arm B	10	rVWF 80 IU/kg	rVWF 80 IU/kg days 1 and 2

rVWF is a single-dose IV infusion given over 5-10 minutes. TA is a single-dose IV infusion given over 10 minutes.

Screening Procedures. Following informed consent, subjects will be screened at the Hemophilia Center of Western PA, by medical history, physical examination, vital signs (height, weight, blood pressure, respirations, heart rate, temperature), and baseline laboratory studies within 3 weeks of the escalating dose study. Baseline labs will include **VWF assays** (VWF:RCo, VWF:Ag, FVIII:C); **coagulation tests** (fibrinogen, d-dimer), **blood counts** (hemoglobin, hematocrit, platelet count); and **iron tests** (Fe, TIBC, ferritin). All tests will be drawn at screening (32-39 weeks' gestation), and all tests except for the iron tests will be drawn on admission for childbirth, at day 1, day 2, and day 21 postpartum. Blood draws will be performed on day 0 pre-delivery by the Magee Labor and Delivery unit as soon as the IV is started. Subsequent blood draws on day 1 and day 2 will be coordinated through HCWP research team. The total blood draw is 49 cc (~2.5 tbsp), including 13 cc (~1 tbsp) at screening; and 9cc (~0.6 tbsp) at the remaining 4 blood draw draws. See Appendix 1.

Up to 30 subjects will be screened to assure 20 subjects are enrolled. Subjects will be randomized to rVWF + TA vs. rVWF alone at delivery. Subjects will receive only the study drug(s) to which they are

randomized, by slow push intravenous infusion. (See Dosing Schema, above). The dose of rVWF will be 80 IU/kg given intravenously over 5-10 minutes at delivery and on day 1 and day 2 postpartum. The dose of TA will be 1 gm (100 mg/mL) given intravenously at an approximate rate of 1 mL/min within 3 hours of delivery. Subjects on Arm A will receive: rVWF 80 IU/kg IV at delivery and on day 1 and day 2 postpartum *plus* TA 1 gm IV within 3 hours of delivery. If bleeding continues after 30 minutes of the first TA dose, a second dose of TA 1 gm IV will be given. Subjects on Arm B will receive: rVWF 80 IU/kg IV at delivery and on day 1 and day 2 postpartum. rVWF will be given by IV infusion by the Magee research nurse just before delivery, and day 1 and day 2 postpartum. TA will be given by IV infusion by the Magee research nurse within 3 hours of delivery. Efficacy assessment, quantitative blood loss (QBL) at delivery, will be determined at delivery, and obtained from the medical record. Safety assessments, including lochia blood loss by pictorial blood assessment chart (PBAC), blood products, transfusion, and other medications will be recorded on the patient diary at 1 day, 2 days, and 21 days postpartum. After each infusion at delivery and on day 1 and day 2 postpartum, any symptoms, allergic reaction, or thrombosis will also be recorded.

The total blood draw for the entire study is 49 cc (~3 tbsp), including 13 cc (~1 tbsp) at screening (32-39 weeks' gestation), and 9 cc (~ ½ tbsp) each on admission for childbirth, at 1 day, 2 days and 21 days postpartum. Blood samples collected during this study will be stored indefinitely at the hemophilia Center of Western PA (HCWP). If other studies are planned, the subject will be re-consented for approval. The stored samples will be under the control of Dr. Machin. There is no plan to use the samples for genetic tests or other tests nor to make them available to secondary investigators.

Laboratory Assays. One blue top (5.0 cc) will be obtained for VWF assays: VWF ristocetin cofactor by platelet aggregometry, VWF antigen by ELISA, FVIII activity by chromogenic assay on an ST4 analyzer; and coagulation assays: fibrinogen by Clauss method, and d-dimer by quantitative assay run in the ITxM/Vitalant Coagulation Laboratory, Pittsburgh. One purple top (4.0 cc) will be drawn for blood counts (hemoglobin, hematocrit and platelets), and one SST tube (4.0 cc) will be drawn for iron studies (iron, TIBC, and ferritin) to be run by standard methods at UPMC University Clinical Laboratories.

Study Termination. A subject will be terminated from the study if any of the following situations arise: the subject develops grade 3 or higher toxicity, allergic reaction, or thrombosis at any time during study.

Study Visit 1: Screening, 32-39 Weeks' Gestation

This visit will take place prior to infusion of study drug(s) in order to confirm eligibility requirements. The following tests or assessment will be performed at the Screening Visit.

- The PI, Dr. Machin or a co-investigator will discuss the study with potential study subjects, answer questions and assure there is adequate time for the potential subject to decide to participate in the study. The potential subject may sign consent or take the consent with them to discuss with family members or other members of the healthcare team. If the potential subject is interested in participating in the study, she may sign the consent document.
- Medical history will include age, all medical diagnoses, current medications, any allergies.
- Vital signs will include blood pressure, temperature, respirations, pulse, weight and height
- Blood draw: a 13 ml (1 tbsp) plasma sample for blood counts and iron studies by UPMC University Clinical Laboratories; and VWF assays and coagulation tests by the ITxM/Vitalant Coagulation Laboratory, Pittsburgh.
- The subject will be randomized and informed of the group to which she is randomized.

Study Visit 2: Admission for Childbirth

This visit begins on admission for childbirth.

- Interim medical history, new diagnoses, medications, allergies.
- Blood draw: a 9 ml plasma sample for blood counts at UPMC University Clinical Laboratories, and VWF assays and coagulation tests by the ITxM/Vitalant Coagulation Laboratory, Pittsburgh.
- Study subject will receive study drug(s) to which they are randomized. Arm A subjects will receive rVWF plus TA, while Arm B subjects will receive rVWF alone. The rVWF is given immediately before epidural or delivery, which is first. TA is given within 3 hours of delivery. If bleeding continues after 30 minutes of the first TA dose (in Arm A), a second dose of TA 1 gm IV will be given.
- Quantitative blood loss (QBL) during C-section and vaginal delivery will be calculated by the labor suite nurse and the mode of delivery will be obtained from hospital medical chart.
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- Assessment for adverse events, allergic reactions, thrombosis, other bleeding
- The study subject will be given a Diary, to record lochia blood loss by pictorial blood assessment chart (PBAC), blood products, transfusion, and concomitant medications daily for up to 21 days.

Study Visit 3: Day 1 Postpartum

The visit occurs at 1 day postpartum.

- Blood draw: a 9 ml plasma sample for blood counts at UPMC University Clinical Laboratories, and VWF assays and coagulation tests by the ITxM/Vitalant Coagulation Laboratory, Pittsburgh.
- Interim medical history, new diagnoses, medications, allergies.
- Diary review: lochia blood loss by PBAC, blood products, transfusion, and concomitant medications.
- Assessment for adverse events, allergic reactions, thrombosis, other bleeding

Study Visit 4: Day 2 Postpartum

The visit occurs at 2 days postpartum.

- Blood draw: a 9 ml plasma sample for blood counts at UPMC University Clinical Laboratories, and VWF assays and coagulation tests by the ITxM/Vitalant Coagulation Laboratory, Pittsburgh.
- Interim medical history, new diagnoses, medications, allergies.
- Diary review: lochia blood loss by PBAC, blood products, transfusion, and concomitant medications.
- Assessment for adverse events, allergic reactions, thrombosis, other bleeding

Study Visit 5: Day 21, End of Study Visit

The visit occurs at 21 days postpartum, at the end of study.

- Blood draw: a 9 ml plasma sample for blood counts at UPMC University Clinical Laboratories, and VWF assays and coagulation tests by the ITxM/Vitalant Coagulation Laboratory, Pittsburgh.
- Interim medical history, new diagnoses, medications, allergies.
- Diary review: estimated lochia blood loss by PBAC, blood products, transfusion, and concomitant medications.

- Assessment for adverse events, allergic reactions, thrombosis, other bleeding.

The blood volume for all tests is 49 cc (~3 tbsp) during this 8-week trial.

3.3 Data Collection and Statistical Consideration.

This is a pilot study comparing rVWF + TA vs. rVWF alone in subjects with Von Willebrand disease, and therefore, comparisons between arms will be descriptive, including mean, median, standard deviation, frequency and percentages. A sample size of at least 20 subjects should provide be sufficient to determine feasibility of enrollment, study drug administration, and data collection for a future phase III trial. Data will be collected by Dr. Machin and her research nursing staff. All data required by the study will be adequately documented in the source documents (hospital records, clinical and office charts, laboratory reports, subject diaries, pharmacy dispensing records).

The Primary Objective is to determine the efficacy of rVWF plus TA vs. rVWF alone in reducing postpartum hemorrhage in women with VWD. The Primary Endpoint is quantitative blood loss (QBL) at delivery. The Secondary Objectives are to evaluate the safety, tolerability, and mechanism of rVWF plus TA vs. rVWF alone in reducing postpartum hemorrhage in women with VWD.

The Secondary Endpoints include safety assessment by lochial blood loss by pictorial blood assessment chart (PBAC) blood products, transfusion, and hysterectomy within 21 days of delivery; and mechanism of PPH reduction by VWF assays, fibrinogen, and d-dimer with 21 days of delivery.

Analysis of endpoints. The Primary Endpoint is based solely on quantitative blood loss (QBL) at delivery obtained by the labor suite nurse and documented by hospital chart. The Secondary Endpoints are based on assessments of safety and the mechanism of hemostasis by rVWF and/or TA. Safety variables, including lochial blood loss by PBAC, blood products, transfusions, and other medications; and the mechanistic variables, including VWF assays (VWF:RCo, VWF:Ag, FVIII:C) and coagulation assays (fibrinogen and d-dimer) will be assessed at 1 day, 2 days, and 21 days postpartum, and where possible, compared with assessment at screening.

Descriptive statistics will be provided for the primary efficacy variable and secondary safety and mechanistic assessment variables, and also by treatment arms. The frequency distribution of the hemostatic and safety efficacy assessments will be presented for each of the study arms.

Blood Sample Storage. Blood samples will be stored indefinitely at the Hemophilia Center of Western PA under the control of Dr. Machin. Samples will be labeled with code numbers, and information linking the code numbers to the subjects' identities will be kept in a separate, locked file at the Hemophilia Center.

Adverse events. The analysis of adverse events, including allergic reaction, thrombosis, and other bleeding, will be based on the number of subjects with adverse events, and incidence rates will be calculated as the number of subjects with an event divided by the number of subjects exposed to drug. Subjects with multiple events will be counted only once in the numerator. For analysis, the highest-grade severity will be considered, and for analysis of duration, the multiple episodes will be summed. Adverse events will be summarized, and each event reported by a subject will be counted repeatedly. The corresponding incidence rates for adverse event episodes will be calculated by the number of adverse event cases over the number of doses. Adverse event incidence rates will be categorized by body system, relationship to study drug, severity of adverse event, age, sex, time of onset of adverse event, and duration of adverse event. Laboratory variables will be analyzed by descriptive statistics.

Sample Size and Power for Pilot Study

Pilot studies require a minimum of nine subjects to prevent an unnecessarily high number of subjects to receive a study drug, but a high enough number to provide insight into safety and efficacy parameters for a study drug.[41] The minimum planned sample size of 20 evaluable subjects also provides adequate power to

evaluate the success and feasibility of the study.[41] The study is considered successful if treatment of fewer than or equal to 6 of the 20 subjects is assessed ineffective or unsafe. The study is considered feasible if procedures, i.e. recruitment, randomization, and study drug administration can be performed successfully.

4.0. Human Subjects

4.1 General Characteristics – Minority Inclusion and Non-Discriminatory Statements.

Because this study evaluates pregnancy in von Willebrand disease, only females ≥ 18 years of age will be included in this study: males and children are excluded. VWD will be defined as VWF:RCo < 0.50 IU/dL (historic) and previous history of bleeding. The racial, gender, and ethnic characteristics of the proposed subject population reflects the demographics of Pittsburgh and the surrounding area and/or the patient population of the University of Pittsburgh Medical Center. Subjects will be recruited in proportion to these demographics. No exclusion criteria shall be based on race or ethnicity.

4.2 Inclusion of Children

Because the study is undertaken to study pregnancy, children are excluded form study.

4.3 Inclusion/ Exclusion Criteria

Inclusion Criteria will include:

1. Pregnant females ≥ 18 years of age
2. Confirmed VWD, as defined by VWF:RCo < 0.50 IU/dL and previous history of bleeding
3. Willingness to have blood drawn
4. Willing to be randomized to one of two treatments at delivery and for 2 days postpartum.
5. Willing to keep a diary for 3 weeks of postpartum bleeding by pictorial assessment chart (PBAC) and any blood products, transfusion, or medications taken.
6. Willing to return at 21 days for final blood draw and review of diary.

Exclusion Criteria will include:

1. Any bleeding disorder other than VWD; or past thrombotic disease of other bleeding disorders.
2. Previous thrombosis, cardiac disease, congestive failure, arrhythmia, hypertension, MI, or stroke.
3. Platelet count < 100,000/ ul.
4. Past allergic reaction to VWF or tranexamic acid.
5. Surgery within the past 8 weeks.
6. Inability to comply with study protocol requirements.
7. Concomitant use of antiplatelet drugs, anticoagulants, or NSAIDs. Aspirin will be allowed for preeclampsia prevention.
8. Treatment with DDAVP, cryoprecipitate, whole blood, plasma or plasma derivatives containing substantial quantities of VWF within 5 days of study.
9. History of renal disease.
10. Inability to comply with study requirements.

Risk/Benefit Assessment: This research involves pregnant women, and thus children are excluded. Among adults, there is some risk with blood draw, but there remains the potential for direct individual benefit. This is based on the balance in favor of potential benefit from receiving a potentially more effective treatment, VWF+TA, over the standard treatment, rVWF alone, with potential risk associated with blood drawing and potential, but rare expected adverse reactions (see below).

4.4 Sources of Research Material. Plasma for all laboratory testing will be collected from subjects enrolled on the study.

4.5 Recruitment Methods and Consent Procedures. It is estimated that 20 subjects will be enrolled at this study site. Pregnant females ≥ age 18 years of age with VWD, defined by VWF:RCo < 0.50 IU/dL (historic) and a previous bleeding history, who fulfill the inclusion and exclusion criteria, and who are cared for at HCWP or Magee outpatient clinic (Pilot Study) or one of the approximately 19 HTCs/obstetric hospitals (Phase III trial) participating in this trial w*ill be eligible for study.* Subjects approached for participation in this study will have VWD and be contacted during routine clinic visits to determine their interest in participating in the study.

Demographic Chart: Targeted Enrollment for Pilot Study

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	0	1
Not Hispanic or Latino	19	0	19
Ethnic Category: Total of All Subjects *	20	0	20
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	19	0	19
Racial Categories: Total of All Subjects *	20	0	20

* The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."

There will be no cold calling. The Site PI will determine the patient's interest in study participation, and, if the patient is interested, the study will be discussed in further detail and the informed consent reviewed. Subjects will be encouraged to take time to decide on participation and ask questions. If subjects decide to take a consent form home for further viewing, discussion will include the purpose, safety issues, and risks and benefits of the study. All questions will be answered prior to and obtaining informed consent. No experimental procedures or interventions will occur until after informed consent is obtained. The investigator's certification statement will be signed at the time consent is obtained. If any new information occurs during the conduct of the study, subjects who have been consented will be informed and will be re-consented with this information at the next visit. A de-identified prescreening/ screening log will be kept, and all reasons for exclusion documented in study source documents and screening log. Subjects who read the consent form are free to refuse enrollment, and participants will be free to withdraw at any time. If subjects wish to withdraw, they may do so by addressing a letter to the principal investigator. Any data collected prior to the time of withdrawal will continue to be used, but no additional information will be collected. Processed blood sample results will continue to be used for the research study; however, remaining samples will be destroyed or used as indicated by subject's letter. The reason (e.g. AE, lost to follow-up, etc.) and date of withdrawal for all subjects withdrawn from this study will be recorded. Subject information obtained by electronic data capture will be stored and managed on the GSPH Data Center website. The IRB may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

Subject eligibility for the study will be determined prior to randomization and the first dose of rVWF and/or TA. Subjects will sign informed consent. Subject screening and enrollment will be conducted by the local Investigator, in communication with the GSPH Data Center web-based data entry system. Subjects will be considered to be enrolled in the study after all assessments have been completed during the Screening period. No subject may receive treatment prior to enrollment and assignment of a unique subject identification number. Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment.

4.6 Risk/Benefit Assessment

Risk to Subjects
There are risks associated with the study drug and having blood drawn. rVWF and/or TA will be administered at delivery and on days 1 and 2 postpartum. All subjects will be asked to report any safety problems or side effects associated with administration of study drug(s).

Risk of Blood Draw
There may be discomfort with drawing blood, which is common, occurring in up to 25%, or 25 in 100 people: this may include pain, lightheadedness, fainting, bruising, or bleeding or infection in the tissue around the vein. This may be alleviated or reduced by applying pressure to the blood draw site for 5 minutes, and assuming a recumbent position, i.e. lying on your back with your head flat and knees bent, if lightheaded.

Risks of Study Drugs:

rVWF and TA
Allergic-type reactions are rarely reported for rVWF, at similar doses as in this study (e.g. 75 IU/kg), and thus, the risk is expected to be uncommon, occurring in < 0.001% or less than 1 in 100,000 people. Allergic reactions for TA are expected to be rare in this study, occurring in <.001%, or less than 1 in 100,000 people. Allergic reactions could include chills, fever, nausea and vomiting, or rarely may include, in decreasing order of severity, death, anaphylaxis (life-threatening difficulty breathing), low blood pressure, heartbeat irregularity, increase in body fluids, paresthesias (numbness or prickling sensation), urticaria (hives), chest tightness, rash, pruritus (itching), edema (swelling), fever, and/or chills. Should these symptoms occur, benadryl, a medication which reduces inflammation, may be given, with close monitoring of these symptoms. Benadryl may cause drowsiness, dizziness or low blood pressure. Subjects will be monitored for these symptoms. No one with a history of allergy (hypersensitivity), an allergic reaction or anaphylaxis associated with either recombinant von Willebrand factor (rVWF, Vonvendi®) or tranexamic acid (TA, Cyclokapron®) will be enrolled. Subjects will be monitored closely for early symptoms and signs of allergic or hypersensitivity reactions, including fever, chills, hives, tachycardia, chest discomfort, and anaphylaxis. Any subject who develops signs or symptoms of an allergic type reaction or anaphylaxis during administration of either study drug will immediately have that study drug stopped and appropriate medical care initiated.

Risk of Thromboembolism/Thrombogenicity
Although rVWF and TA may increase coagulation factor levels, they are rarely, if ever, associated with the development of thromboembolic complications. There is the unlikely possibility, < 0.001%, or less than 1 per 100,000 people, that either drug could cause a clot in the vein (thrombosis) with swelling or pain; or a clot in the lung (pulmonary embolus) with dyspnea or hemoptysis. Pregnancy is associated with increased risk of thromboembolism, but this is rarely seen in women with VWD: study drug will be limited to the first 2 days postpartum, per standard of care, as this is also the greatest time of postpartum bleeding. This risk will be very carefully monitored clinically. Should thrombosis symptoms occur measures considered standard of care would be

implemented to prevent clots: these include either compression stockings, which are support-like stockings, and/or sequential compression devices (SCDs). SCDs are blanket-like Velcro-devices which are placed on the legs to promote blood flow and prevent clots from forming in the leg veins. Should a clot occur, treatment would primarily consist of stopping the study treatment and/or removing the line in which it was given, if that is the source of the clot, as soon as possible. Should a bleeding episode occur during the study, the subject will be treated with rVWF or another hemostatic agent prescribed by the subject's physician.

Diphenhydramine (Benadryl)
Common Side Effects include sedation, sleepiness, dizziness, disturbed coordination, pain in the abdomen, and excess fluid or mucus.

Uncommon Side Effects include hives, rash, anaphylactic shock, sun sensitivity, excessive perspiration, chills, dryness of mouth, nose, and throat, low blood pressure, headache, rapid or irregular heartbeat, low blood cells, low white blood cell count, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, pins and needles feeling, blurred vision, double vision, a sensation of whirling and loss of balance (vertigo), ringing in the ears, inflammation of the inner ear ,nerve pain, convulsions, loss of appetite, nausea, vomiting, diarrhea, constipation, urinary frequency, difficult urination, urinary retention, early menses, tightness of chest or throat and wheezing, and nasal stuffiness.

Other Risks
Bleeding symptoms may occur in VWD unrelated to this study, usually with trauma, but sometimes spontaneously, without cause. Further, because individuals with VWD are enrolling on a trial in which study drug(s) will be administered by infusion, there is a risk of bleeding at the infusion site. Subjects should contact their physicians if this occurs and/or seek medical attention. In the event that bleeding at the infusion site cannot be stopped with pressure, it may be necessary to use a stitch or an adhesive material to stop the bleeding. The devices used to administer the stitch or adhesive may cause the following negative side effects: bleeding, a build-up of blood known as a hematoma, infection, allergic reaction, nerve injury, and swelling.

Risk of future testing of stored samples
Breach of confidentiality which could affect future insurability, employability, or reproduction plans, or have a negative impact on family relationships, and/or result in paternity suits or stigmatization. In order to reduce risks of disclosure or breach of confidentiality, the research related documents, blood samples and clinical information stored in subject research files will be assigned an alphanumeric (letters and numbers) identifier (that do not contain personal identifiers). For this study, a linkage key for linking this number and the subject's name will be kept at each site under lock and key by the PI and his/her research staff.

Collection of private health information and participant diary
There is also a potential for possible risk of breach of confidentiality of collected information. To minimize this risk, study participation and related information will be protected to maintain confidentiality. Blood samples and clinical history will be assigned an alphanumeric identifier and the key for linking this number with subject identity will be kept at each site under lock and key by the PI and his/her research staff. The de-identified information in this study will be placed into a secure, web-based data base at University of Pittsburgh Graduate School of Public Health (GSPH) Data Center. If the investigator publishes research information, subject names will not be identified.

Potential Benefits

The subjects will be under close supervision during the study period. After administration of rVWF or TA it is anticipated postpartum bleeding frequency will be decreased from the untreated state. For women with VWD, it is already established rVWF and TA may reduce postpartum bleeding, but whether one agent is more effective or better tolerated than the other is not known.

Risk Benefit Ratio

The risk/ benefit ratio indicates the value of the information to be gained outweighs the potential risks of participation in the trial as 1) risks associated with rVWF and TA are low, importantly thrombosis risk is <0.4% with VWF, based on data from the literature; and 2) individuals with cardiac disease, hypertension, MI, stroke, thrombosis, or seizure are excluded from the trial. Thus, the risk/benefit ratio of participating in the trial outweighs the risk of gained outweighs the potential risks of participation in the trial.

5.0 Risk Management Procedures

Data Safety Monitoring Plan (DSMP)

The local Data Safety Monitoring Plan for this trial will include the following requirements:

1. This study will identify, monitor, and report adverse events (AE) and unanticipated problems (UP).
2. Expedited reporting to the IRB is required for unanticipated problems (UP) or unexpected serious adverse events (SAE) that may be related to the study protocol as follows:

Any event or problem that is unexpected AND possibly, probably, or definitely related to study participation AND one of the following:

- Is fatal, life-threatening, or serious (SAE + UP) ..... REPORT within 7 calendar days
- Suggests greater risk of harm to study participant(s) than..... REPORT within 30 calendar days was previously known or recognized

3. Expedited SAE/UP reporting to the IRB should include study and grant number, PI, description of the event or problem, why it merits expedited reporting, dates the event was reported to IRB, FDA and other governing bodies, and any corrective action planned or taken in response to the event or problem, e.g. study suspension, consent or protocol changes, additional training or security measures.
4. Reporting is required by the investigator to and following the guidance of any other applicable oversight bodies, but not limited to IRB, local DSMB and FDA. All communication from these oversight bodies regarding any applicable SAE/UP must be reported to IRB according to the Data and Safety Monitoring Policy.

The PI, Dr. Machin, the Co-Investigators, and the HCWP nurse coordinator(s) will be responsible for ongoing monitoring of all recruitment, data collection and subject confidentiality procedures at this site. They will meet at least bi-weekly to review all aspects of the study. Subjects will be closely monitored by the PI, research and clinical staff to ensure subject safety and to ensure that procedures are in place to maintain privacy and confidentiality, progress of study, integrity of the data, procedure reviews and for discussion of pertinent scientific literature or events which could affect the benefit to risk ratio. All serious and unexpected adverse events and/or major breaches of confidentiality will be reported to the IRB according to regulations outlined in the IRB *Reference Manual for the Use of Human Subjects*. All AE's, SAE's generated from the Hemophilia Center of Western PA will be sent following CRF and eCRF reporting guidelines to IRB. A report summarizing the above local DSMP activities will be submitted to the IRB at the time of annual renewal.

Data will be reviewed on an ongoing basis by the local Data Safety Monitoring Committee (DSMC). A Data Safety Monitoring Committee (DSMC) will review all data collected on the study. All DSMC members will have voting rights. The DSMC will review data for all subjects enrolled in the study protocol and determine if the risk benefit ratio is sufficiently favorable that it is appropriate to continue the trial.

The events are:

- A subject develops anaphylaxis in association with administration of rVWF and/or TA
- A subject develops a thrombotic event in association with the administration prophylaxis with the exception of intravenous (IV) infusion site thrombophlebitis.
- A subject develops severe or severe bleeding requiring prolonged and/or intense treatment exceeding study-related dosing.
- A subject develops a Grade 2 or greater allergic reaction in association with rVWF and/or TA defined as follows using the CTCAE grading.[40]
    - Grade 2 Transient flushing, rash, or drug fever $\geq$ 38º C.
    - Grade 3 Symptomatic bronchospasm; with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension
    - Grade 4 Anaphylaxis

  In addition to halting enrollment and further treatment, such an event will be handled as a serious adverse event (SAE) and reported in an expedited time frame to the FDA. The data concerning the event and subject with input from the site HTC Co-Investigator will be reviewed by the DSMC along with all other available data to determine appropriate follow-up, with a decision to continue enrollment and treatment of subjects at that time. If the decision is made to discontinue the study, the Co-Investigators will be notified and the appropriate final study evaluations (Final Visit) will be performed on all subjects enrolled in the study at that time.

  Additionally, the following may also stop further subject enrollment and treatment.
- The DSMC warrants temporary suspension of enrollment for further review of data generated to date.
- The PI determines that a medically important event warrants further evaluation by the DSMC. In these cases the required follow-up as determined by the PI and/or DSMC will be performed. The DSMC will determine if it is appropriate to reinitiate enrollment in the study. The IRB will be informed of such decisions.

Local Adverse Event Reporting

All adverse events experienced by study subjects from the time of dosing until 30 days after administration is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment.

The serious AE reporting procedures are based on the "Cancer Therapy Evaluation Program: Common Terminology Criteria for Adverse Events" (CTCAE) v 4.03, June 14, 2010.[40] Subjects will report to HTC co-investigator or to the HTC nursing coordinator, any AE or SAE. AE's will be classified as mild (does not interfere with routine activities), moderate (interferes somewhat with routine activities), or severe (impossible to perform routine activities). The following algorithm will be used to assess the causality of all AE's:

- Not related: The event can readily be explained by factors not involving rVWF and/or TA, and a temporal relationship with rVWF and/or TA, does not exist.
- Possibly related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of rVWF and/or TA, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- Probably related: The temporal relationship between the administration rVWFand/or TA is compelling, and the event cannot be explained by the subject's medical condition or other therapies.
- Related: The event follows a reasonable temporal sequence from administration of rVWF and/or TA follows a known or suspected response pattern to rVWF and/or TA, is confirmed by improvement upon stopping the agent (de-challenge) and reappears upon repeated exposure to rVWF and/or TA.

All AEs, regardless of severity, will be followed up by HTC Investigator until satisfactory resolution. All subjects experiencing AEs will be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report will be supplied, if possible. Withdrawal from the clinical study and therapeutic measures shall be at the discretion of the investigator.

As required by the University of Pittsburgh Institutional Review Board, if there is an unexpected, serious internal adverse event (life threatening or fatal) that is determined to be associated with rVWF and/or TA, it will be reported to the IRB within 24 hours. If the event is not serious, unexpected or related to either agent, it will be reported within 5 days. External adverse events that are unexpected, related to either agent and determined to place the subject at greater risk than previously recognized, will be reported within 10 working days of notification.

Adverse Event (AE) Reporting at sites:

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE
- The relationship of the event to study treatment
- The severity of the event

An AE is any untoward medical occurrence in a subject in whom a pharmaceutical product is administered and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not related to the pharmaceutical product.

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- in the view of the Investigator, places the subject at immediate risk of death (a life-threatening event), but does not include an event that, had it occurred in a more severe form, might have caused death
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity, or
- results in a congenital anomaly/birth defect.

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

In this study, the following events are considered medically important and must be reported as SAEs:

- A subject develops other bleeding in association with administration of rVWF and/or TA.
- A subject develops anaphylaxis in association with administration of rVWF and/or TA.
- A subject develops a thrombotic event in association with the administration of rVWF and/or TA, with the exception of intravenous (IV) infusion site thrombophlebitis.
- A subject develops a Grade 2 or greater allergic reaction in association with administration of rVWF and/or TA defined as follows using the CTCAE Evaluation.
    - Grade 2 Transient flushing, rash, or drug fever $\geq$ 38º C.

- Grade 3 Symptomatic bronchospasm; with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension
- Grade 4 Anaphylaxis

Any SAE experienced by the subject from the time of dosing until 30 days after rVWF and/or TA administration is to be recorded on an SAE Form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to the PI. Any SAE ongoing when the subject completes the study or discontinues from the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

A serious pre-treatment event associated with the conduct of the study experienced by the subject after signing the ICF, but before administration of study treatment is to be recorded on the Serious Adverse Reaction (SAE) CRF and faxed (and electronically uploaded) to the PI within 24 hours of the study site staff becoming aware of the event.

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site will formally notify the PI within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are followed. A death must be recorded on the appropriate CRF and electronic CRF (eCRF). All causes of death will be reported as SAEs.

Reporting Information for SAEs

Any SAE that occurs after any subject receives rVWF and/or TA and any serious pre-treatment events must be reported to the PI within 24 hours of the study site staff becoming aware of the event. This report must be submitted regardless of whether or not the subject has undergone any study-related procedures or received study treatment and *regardless of severity or relationship to study treatment.* To report initial or follow-up SAE information and serious pre-treatment medical event information, enter the information in the CRF and web-based CRF. If the database is not available, fax a completed SAE form to the following or, if fax is not possible, call the number below to report the information. *Emergency Contact Numbers:* Fax: 412-209-7281; Phone: 412-209-7288 (daytime); Phone: 1-888-990-1100 (evening and weekends)

Safety Classifications and Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Relationship of Event to Study Treatment

Unrelated	Any event that does not follow a reasonable temporal sequence from administration of study treatment *AND* that is likely to have been produced independently by the subject's clinical state or other modes of therapy administered to the subject.
Unlikely	Any event that does not follow a reasonable temporal sequence from administration of study treatment *OR* that is likely to have been produced by the subject's clinical state or other modes of therapy administered to the subject.
Possibly	Any reaction that follows a reasonable temporal sequence from administration of study treatment *OR* that follows a known response pattern

	to the suspected drug *AND* that could not be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.
Related	Any reaction that follows a reasonable temporal sequence from administration of study treatment *AND* that follows a known response pattern to the suspected drug *AND* that recurs with re-challenge, *AND/OR* is improved by stopping the drug or reducing the dose.

Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

A prescheduled or elective procedure or a routinely scheduled treatment will not be allowed during the study period.

7.0 Data Sharing Plan

This study will be conducted in accordance with the following publication and data sharing policies and regulations per NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. The final peer-reviewed journal manuscripts arising from this study will be submitted to the digital archive PubMed Central upon acceptance for publication. This study will also comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Researchers will be able to locate and access data and/or other specimens from the VWD-WOMAN Trial by formal application to the VWD-WOMAN Trial Team.

8.0 Costs and Payments.

8.1 Research Study Costs. All costs associated with this study are experimental, as described below, including laboratory tests, out-patient hospitalization, study drugs, drug injections and infusions, blood sampling. The subject and insurer will not be billed for any research only services. The study will provide the study drug(s), rVWF (Vonvendi®) and TA (Cyclokapron®), drug administration, blood sampling, and coagulation testing at no cost. The subject and insurer will not be billed for any of these costs. The history and physical exam and monitoring will be provided at no cost by the investigators. Subjects or their third-party payer will be responsible for the costs associated with any routine medical care not part of this experimental study, should such costs arise. The subject will be responsible for any applicable copays, coinsurances and deductibles.

8.2 Research Study Payments. Subjects will receive remuneration for costs related to their participation

to help defray the cost of meals, travel, and time lost from work. There will be no additional costs to for participation in this study beyond the charges for routine medical care. The study will be funded by Takeda. Compensation is based on study visits completed. Subjects will receive $50 for completing the initial screening visit (32-39 weeks' gestation); $100 at admission for childbirth; and $50 each at 1 day and 2 days postpartum; and $150 on the Final Visit on Day 21, for a total of $400.00. If a subject does not complete any part of the scheduled study visits, compensation for missed visits will not be made. Subjects will be paid upon completion of the study. If, for whatever reason a subject completes part, but not all of the study, the terms of payment will be determined by the visits completed.

9.0 Research Needs to be Provided by Investigator's Laboratory or Outside Laboratory: Von Willebrand factor assays (VWF:RCo, VWF:Ag, FVIII:C) and coagulation testing (fibrinogen, d-dimer) will be performed by the ITxM/ Vitalant Coagulation Laboratory under the direction of Mr. Mike Meyer; and blood counts (hemoglobin, hematocrit, platelets) and iron studies (Fe, TIBC, ferritin) will be performed by UPMC Clinical Laboratories.

10.0 Qualifications of Investigator.

Dr. Niki Machin is a Clinical Instructor of Medicine in the Division of Hematology/Oncology , and is working with Dr. Ragni and to conduct in the proposed trial. She has completed Research Fundamentals training.

Dr. Craig Seaman is an Assistant Professor of Medicine in the Division of Hematology/Oncology and engaged in research and patient care in VWD and other disorders of congenital hemostasis and thrombosis.

Dr. Maria Brooks is a Professor of Epidemiology and statistician at the Graduate School of Public Health Data Center where she has served as PI of Data Coordinating Centers (DCC) for NHLBI trials and has worked closely with Dr. Ragni on several clinical trials in bleeding disorders.

11.0 Funding Support: Takeda

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APPENDIX

SCHEDULE OF EVENTS

Schedule of Events					
Study Week	**-4**	**0**	**0**	**0**	**3**
Study Visit	**1**	**2**	**3**	**4**	**5**
Event	32-39 Weeks'	Admission Childbirth	Day 1	Day 2	Day 21

	Gestation				
Screening, Consent	**X**				
Clinical Assessment					
Medical History	**X**		**X**	**X**	**X**
Vital Signs	**X**				
Mode of Delivery		**X**			
Randomization	**X**				
End of Study					**X**
Laboratory Assessment					
Blood Counts: Hemoglobin, Platelets	**X**	**X**	**X**	**X**	**X**
Iron Tests: Fe, TIBC, Ferritin	**X**				
VWF Assays: VWF:RCo, VWF:Ag, VIII:C	**X**	**X**	**X**	**X**	**X**
Coagulation Assays: Fibrinogen, D-dimer	**X**	**X**	**X**	**X**	**X**
Primary Endpoint Measure					
Quantitative Blood Loss at Delivery		**X**			
Secondary Endpoint Measures					
Lochial blood loss by PBAC			**X**	**X**	**X**
Diary: Blood products, transfusion, medications			**X**	**X**	**X**
Safety: Hysterectomy, thrombosis			**X**	**X**	**X**
Adverse Events					
Allergic reaction		**X**	**X**	**X**	**X**
Thrombosis		**X**	**X**	**X**	**X**
Bleeding (other)		**X**	**X**	**X**	**X**