# A PHASE IA STUDY OF VGA039, A PROTEIN S–TARGETING MONOCLONAL ANTIBODY, IN INDIVIDUALS WITH VON WILLEBRAND DISEASE DEMONSTRATES CONCENTRATION-DEPENDENT INCREASES IN THROMBIN GENERATION FOR REDUCING BLEEDING


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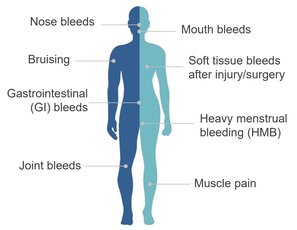
## INTRODUCTION

### VWD Patients Have High Treatment Burden But Limited Treatment Options

- Von Willebrand Disease (VWD) affects up to 1% of the population
- Patients with VWD experience heterogeneous bleeding manifestations and severity
- Problems with platelet adhesion/activation (deficient/defective VWF) & clot stability (limited FVIII half-life)

#### VWD Presentation



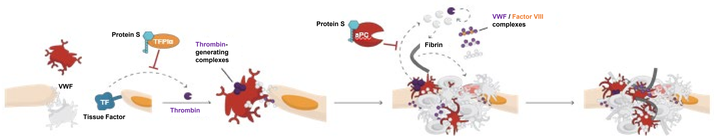

#### Current Treatments are Burdensome and Limited

- Frequent IV factor concentrate infusions (2-3 times/week)
- Adjunctive treatments with short-lived therapeutic durability and/or substantial side effects
  - DDAVP
  - Anti-fibrinolytics
  - Hormonal therapies for heavy menstrual bleeding

#### Non-Factor Therapies May Fulfill Unmet Needs

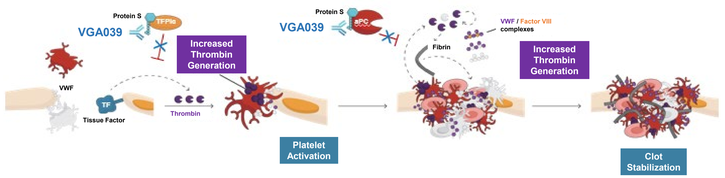
- Less frequent dosing and more convenient administration than factor concentrate prophylaxis to reduce bleeding
- Potential to provide hemostatic balance in various bleeding disorders

### In VWD, Bleeding is Associated with Insufficient Platelet Adhesion and Unstable Clot Formation




In VWD, qualitative and/or quantitative defects in VWF, the carrier protein for FVIII, result in VWF and FVIII deficiencies, creating a coagulation imbalance characterized by insufficient platelet adhesion, thrombin generation, fibrin deposition, and unstable clot formation

### VGA039 Rebalances Coagulation in VWD by Increasing Thrombin Generation, Platelet Activation, and Clot Stabilization to Decrease Bleeding




VGA039 works independent of VWF, blocking Protein S cofactor activity for tissue factor pathway inhibitor alpha- (TFPIα-) and activated Protein C (APC)-mediated inhibition of thrombin generation, thereby rebalancing thrombin generation during the initiation and propagation phases of coagulation to decrease bleeding

**VGA039-CP001, PART 2**

**NCT05776069**

**VIVID 2**

## OBJECTIVE

- To evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy (exploratory) of a single ascending dose of subcutaneous VGA039

## METHODS

### VIVID 2: Subcutaneous (SC) Single Ascending Dose (SAD) in VWD Patients

#### Study Design

- Open-label, single ascending dose of SC VGA039
- IV cohorts (Cohorts A-D) skipped, per Sponsor decision
- Starting SC dose: 3.0 mg/kg (maximally tested SC dose in healthy volunteer SAD)
- 3 patients per cohort, potential to expand by 2-6
- Dose escalate until sufficient pharmacodynamic (PD) effect observed or dose escalation stopping criteria met
  - D-dimer >4x upper limit of normal (2.0 µg/mL), in 2 consecutive results separated by at least 24 hours and in at least 2 subjects

#### Key Inclusion/Exclusion Criteria

- Males & females, ages 18-60
- Symptomatic VWD (history of bleeding or bruising) of any type/sub-type
- No history of thromboembolism
- Negative thrombophilia testing
- FVIII activity ≤50 IU/dL

## RESULTS

### Range of Ages, VWD Types/Sub-Types, FVIII Activities, & Body Weights Represented

| Subject ID | Cohort | SC Dose | Sex | Age (Years) | Type/ Sub-Type | Baseline FVIII Activity | Weight (kg) |
|---|---|---|---|---|---|---|---|
| 08-002 | E | 3.0 mg/kg | Male | 51 | Type 2A | 26 IU/dL | 77.2 |
| 05-001 | E | 3.0 mg/kg | Female | 31 | Type 2M | 25 IU/dL | 64.2 |
| 16-001 | E | 3.0 mg/kg | Female | 37 | Type 3 | 27 IU/dL | 115.7 |
| 15-002 | F | 4.5 mg/kg | Male | 24 | Type 3 | 5 IU/dL | 100.0 |
| 01-093 | F | 4.5 mg/kg | Male | 28 | Type 1 + Mild hemophilia A | 9 IU/dL | 72.0 |
| 13-001 | F | 4.5 mg/kg | Female | 21 | Type 2M | 23 IU/dL | 46.7 |
| 17-002 | F | 4.5 mg/kg | Male | 52 | Type 3 | 2 IU/dL | 153.7 |

IV dose cohorts (Cohorts A-D) skipped, given VGA039's high bioavailability (≥98%)[3]

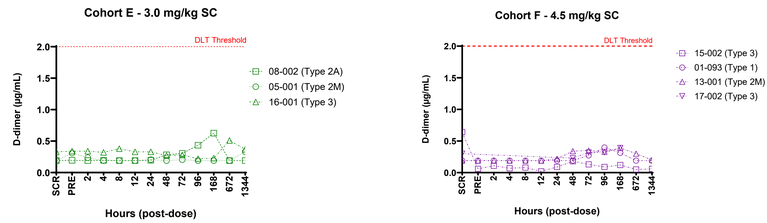
### Summary of Dosing & Safety

- A total of 7 VWD patients have been dosed in 2 cohorts (3 patients dosed with VGA039 in Cohort E & 4 patients in Cohort F)
  - No Grade 2 or higher AEs
  - No study drug-related AEs
  - No remarkable abnormalities in laboratory, physical exam, or ECG parameters
  - No injection-site reactions reported
  - No thromboembolic events reported
  - No dose escalation-stopping criteria met

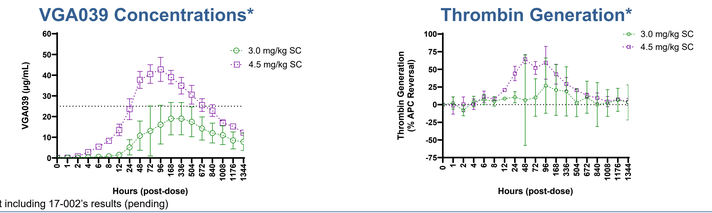
ABR=annualized bleeding rate; AE=adverse event; DDAVP=desmopressin; DLT=dose-limiting toxicity; ECG=electrocardiogram; FVIII=factor VIII; IV=intravenous; VWF=von Willebrand factor.

## RESULTS (CONTINUED)

### No D-dimer Dose-Limiting Toxicities with Single 3.0 or 4.5 mg/kg SC Dose

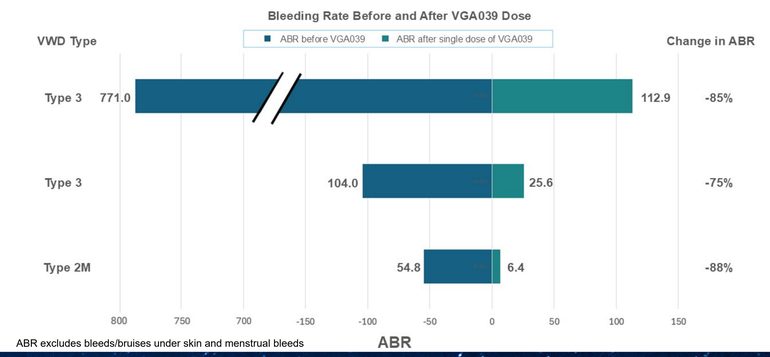



### Single 4.5 mg/kg SC Dose: VGA039 Concentrations Associated With Increased Thrombin Generation Sustained for ~4 Weeks




* Not including 17-002's results (pending)

### Marked ABR Reductions in Three 4.5 mg/kg Subjects With Historical ABRs >50




ABR excludes bleeds/bruises under skin and menstrual bleeds

## CONCLUSIONS

- VGA039 was safe and well tolerated in this SC SAD study in VWD subjects across all types
- ABR reductions observed in patients achieving VGA039 plasma concentrations associated with increased thrombin generation and in the absence of DLTs
- Additional dose cohort (Cohort G: 7.0 mg/kg) underway
- SC multi-dose VGA039 investigation is planned


**References**: 1. Sidonio RF et al. *J Blood Med*. 2020;11:1-11. 2. The diagnosis, evaluation, and management of von Willebrand disease. NIH Publication No 08-5832. 2007. 3. Schorgenhofer C et al. Accessed https://isth2024.eventscribe.net/fsPopup.asp?efp=R0tKSkNBT0ExNjMzNg&PresentationID=1433044&rnd=0.5960945&mode=presInfo on November 10, 2024.