VELORA Pioneer: Preliminary safety and PK/PD data of a first-in-human study of HMB-002 in Type 1 Von Willebrand disease

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ISTH 2025 ▪ 33rd Congress of the International Society on Thrombosis and Haemostasis ▪ Washington, United States ▪ June 21-25, 2025

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Shareholder	No relevant conflicts of interest to declare
Grant / Research Support	CSL Behring, Sobi, Takeda, Roche
Consultant	CSL Behring, Pfizer, Takeda, Sobi, Sigilon, Idogen, LFB
Speaker honoraria	CSL Behring, BioMarin, Pfizer, Sobi
Employee	No relevant conflicts of interest to declare
Other	No relevant conflicts of interest to declare

Von Willebrand Disease (VWD): A Bleeding Disorder with Unmet Needs

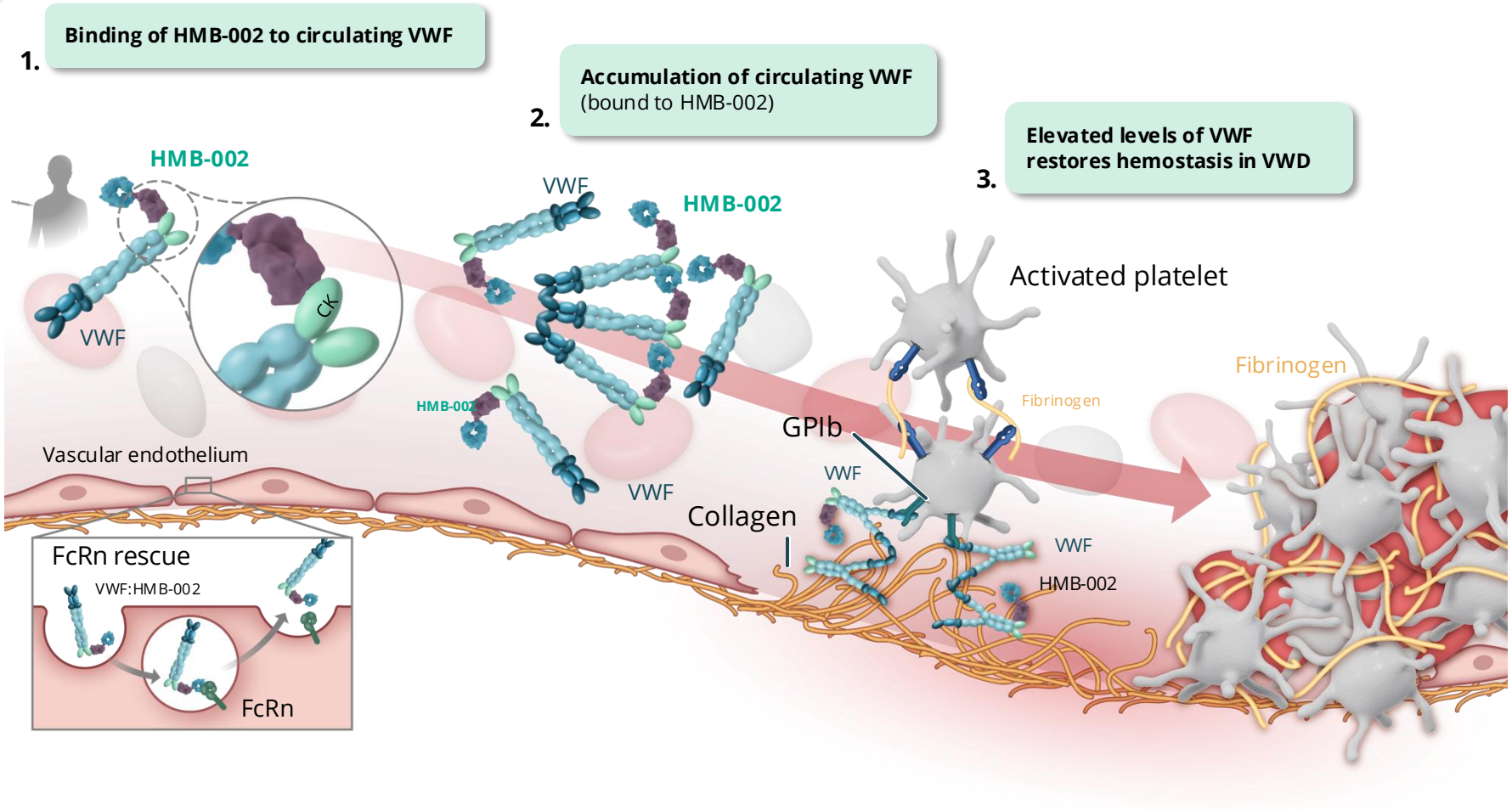
- Von Willebrand Factor (VWF) is a multimeric protein critical to primary hemostasis, through binding of collagen and platelets and to secondary hemostasis by carrying factor VIII
- VWD is the most common inherited bleeding disorder affecting about 1% of population
- VWD arises from a quantitative deficiency (<1-50%) in VWF or a defect in protein function
- Patients experience frequent bleeding events with significant associated physical and psychosocial impacts[1]
- Raising VWF ≥1.5 to 2x associated with decreased bleed scores and bleeding severity[2-5]
- Current treatments that raise VWF have short duration (DDAVP) or frequent IV administration (factor concentrates), limiting their use for preventing bleeding in patients with VWD

1. Khair et al. (2025) ISTH Congress. Poster PB1432 & PB1460 (VWD 360 Study); 2. Sadler JE, et al. Hematology Am Soc Hematol Educ Program. 2009; 3. Tosetto A, et al. J Thromb Haemost. 2006; 4. Sadler JE, et al. Blood. 2003; 5. Federici AB, et al. Blood. 2014.

HMB-002: Monoclonal antibody to VWF designed to increase VWF and FVIII

Features of HMB-002

- HMB-002 is a monovalent antibody, administered subcutaneously
- HMB-002 binds at VWF CK domain
- Engages FcRn receptor and undergoes recycling via FrRn pathway, delaying clearance of VWF[1]
- VWF accumulates, elevating both VWF and FVIII levels
- Monovalent design avoids VWF cross-linking
- Preclinical studies demonstrated 1.5-2x elevation of VWF/FVIII, preservation of VWF functions, and no adverse findings at any dose level[2]



1. Häger M, et al. ISTH 2025. Oral OC 08.4; 2. Rasmussen C, et al. ISTH 2025. Oral OC 59.5

Phase 1/2 Study of HMB-002 in Individuals with Type 1 VWD

VELORA Pioneer

Objectives

- Phase 1 single ascending dose to evaluate PK, PD and safety of HMB-002
- Exploratory efficacy in A3,A4 – prospective bleed/treatment collection pre/post dose

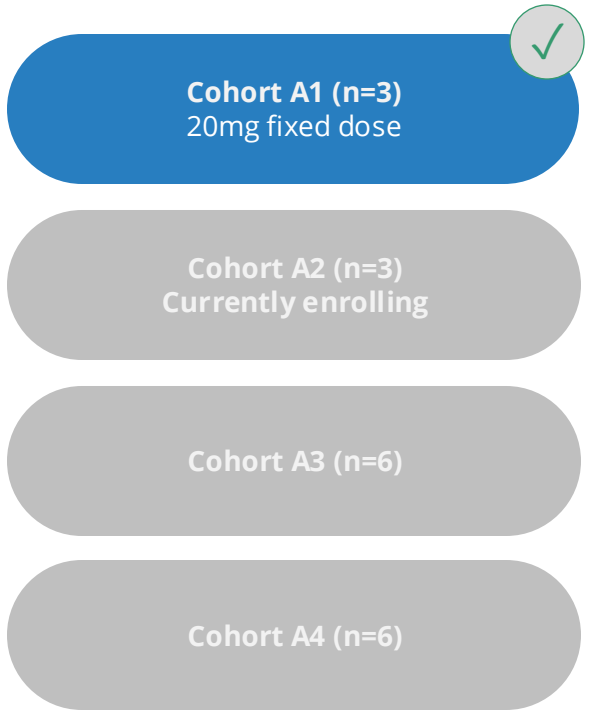
Key inclusion criteria

- Type 1 VWD
- VWF activity <40% at baseline
- FVIII activity <70% at baseline
- Males and females
- Age 18 to 65 years

Key study stopping rules

- ≥1 SAE related to study drug
- ≥2 Grade 3 or above AEs related to study drug

Part A*: Single Ascending Dose



Adaptive protocol design enabling:

- Cohort expansion up to n=12 for cleared doses; addition of cohorts
- PK/PD model-based modifications of:
  - Dose
  - Duration to match predicted PD
  - FVIII and VWF baseline levels to target FVIII < 150%; VWF < 200%

Study Progression:

- Dose escalation proceeds if minimum patients dosed per cohort and no stopping rules triggered
- Multi-dose portion of the study (Part B) to open following dose selection from Part A

Abbreviations: PD, pharmacodynamics; PK: pharmacokinetics; VWD, von Willebrand disease.
Full eligibility criteria available at ClinicalTrials.gov (NCT06754852). Interim data cutoff as of 15th April 2025 for safety data and 10th June 2025 for PK/PD data

Baseline and Demographics

Cohort A1 (n=3)		
Age	Mean (min, max)	38.7 (27, 62)
Sex, n (%)	Female	1 (33.3)
	Male	2 (66.7)
Race, n (%)	White	3 (100)
Weight (kg)	Mean (min, max)	73.53 (61.8, 87.6)
Baseline VWF:Ac (%)	Mean (min, max)	24.2 (21.1, 26.0)
Baseline VWF:Ag (%)	Mean (min, max)	23.6 (23.0, 23.9)
Baseline FVIII:C (%)	Mean (min, max)	43.7 (42.1, 46.8)

Abbreviations: VWF:Ac, von Willebrand factor activity; VWF:Ag, von Willebrand factor antigen; FVIII:C, Factor VIII coagulant activity

Safety Summary: Cohort 1

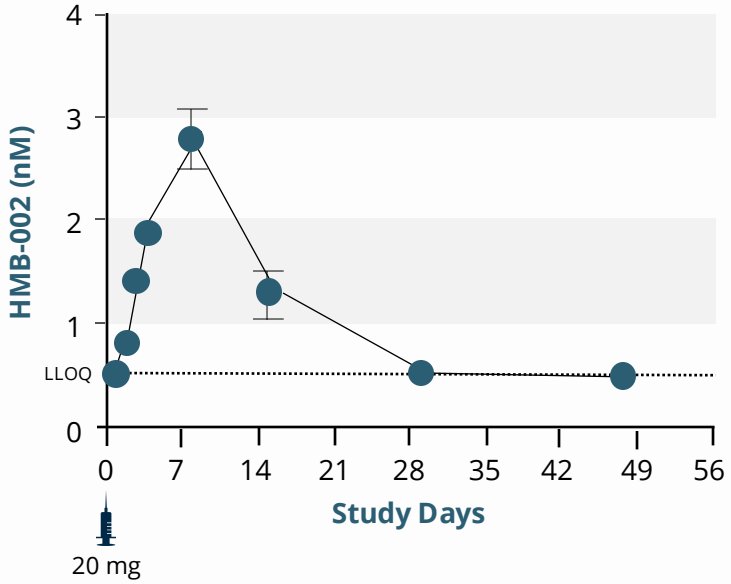
- N=3
- 20 mg dose
- 56-day observation period following single dose
- No adverse events reported, including:
  - No thrombotic events
  - No thrombocytopenia or changes in D-dimer levels
  - No injection site or hypersensitivity reactions
  - Anti-drug antibody (ADA) testing negative at all timepoints
  - No changes in inflammatory markers (C3a, C5a, cytokines)

Abbreviations: APTT, activated partial thromboplastin time; ADA, anti-drug antibody; C3a/C5a, complement fragments 3a and 5a.

Lowest planned dose (20 mg) of HMB-002 Elevates VWF and FVIII ~1.5-fold

Plasma HMB-002

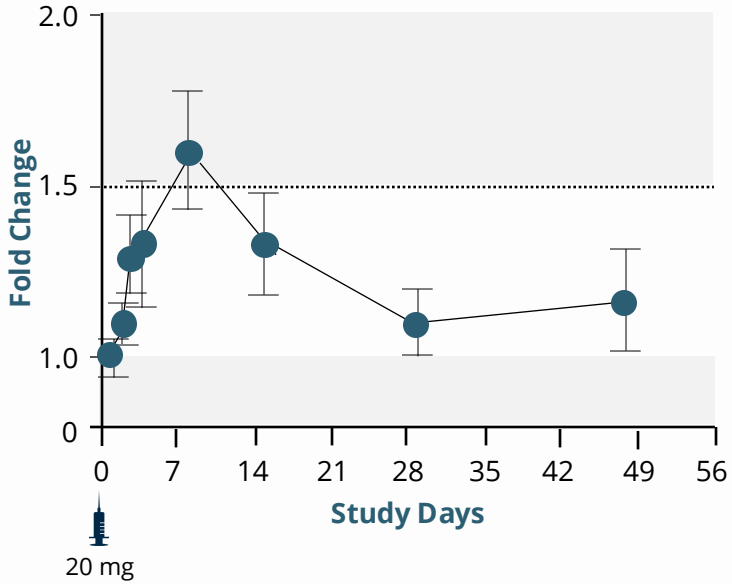
Mean (SEM) Plasma HMB-002



Tmax Day 8
(161 hours)

Plasma VWF Antigen

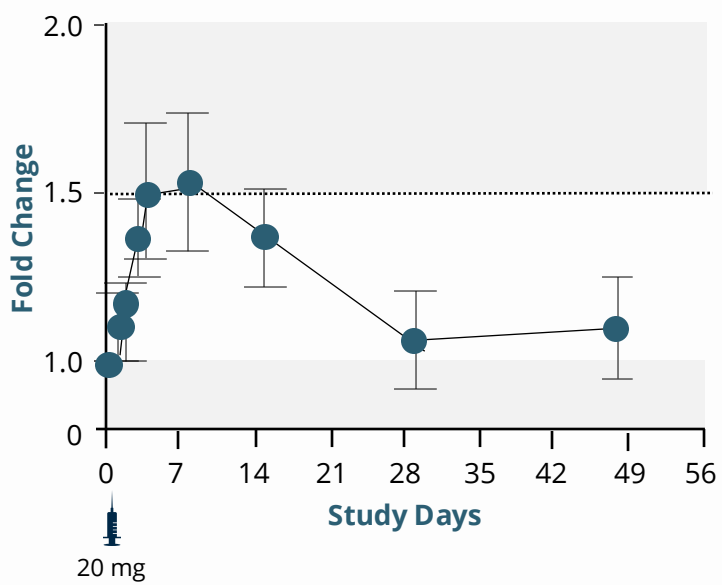
Mean (SEM) Plasma VWF Antigen



Peak >1.5x
Tmax Day 8
28 days above baseline

Fold change FVIII:C

Mean (SEM) Plasma FVIII Activity



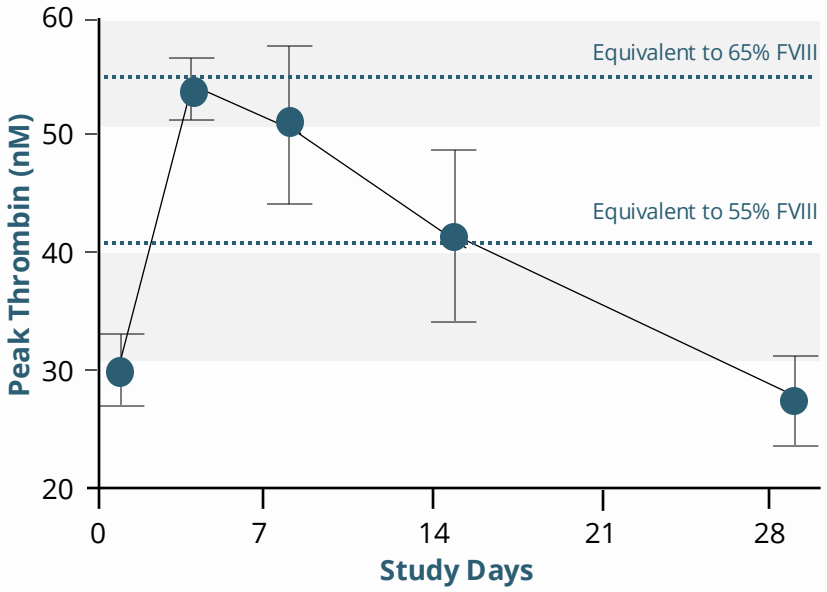
Peak >1.5x
Tmax Day 8
28 days above baseline

Abbreviations: SEM, standard error of the mean; LLOQ, lower limit of quantification; VWF, von Willebrand factor; FVIII, coagulation factor VIII; Tmax, time to maximum concentration.

HMB-002 improves Thrombin Generation and Normalizes APTT

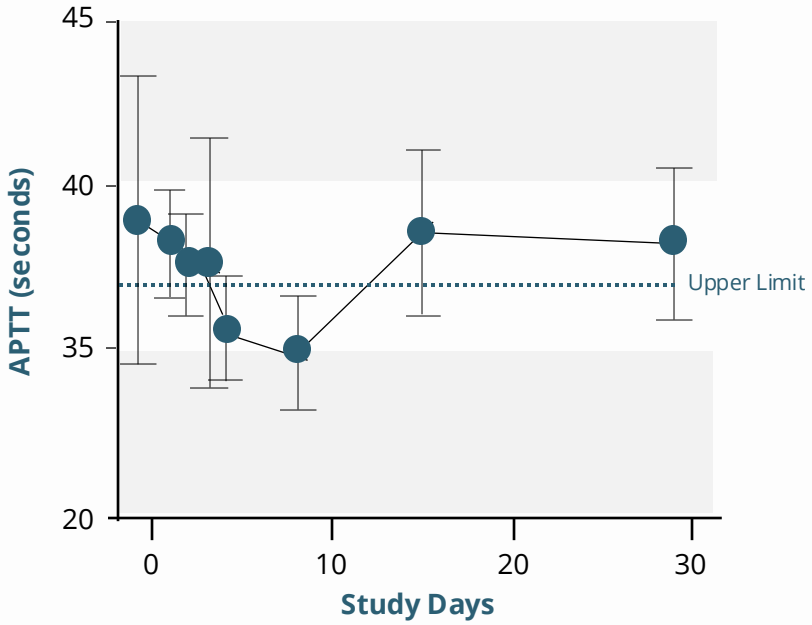
Thrombin Generation

Mean (SEM) Peak Thrombin Levels (nM)



APTT Improvement

Mean (SD) Activated Partial Thromboplastin



- TG elevation and APTT normalization maximal between Days 5 and 14, coinciding with Tmax FVIII elevation
- Peak TG is at levels equivalent to approximately 55-65% FVIII*
- TG elevation and APTT improvement demonstrate impact on secondary hemostasis

Abbreviations: APTT, activated partial thromboplastin time; TG, thrombin generation; SEM, standard error of the mean; SD, standard deviation..
Methods: Calibrated Automated Thrombogram, 0.5 pM tissue factor, platelet-poor plasma. Note: Exploratory endpoint in Phase 1 (n=2 evaluable; one participant excluded due to baseline interference)
*Based on control experiments where control plasma has been spiked with increasing FVIII concentrations to establish Peak Thrombin Generation and ETP

Conclusions

- At the lowest dose cohort (single dose, 20mg HMB-002), 1.5-fold elevation of VWF and FVIII is achieved
- VWF and FVIII levels remained elevated above baseline for 28 days post-administration
- No adverse events were recorded
- Safety and pharmacodynamic data support continued dose escalation to explore increased accumulation and duration of PD response with higher doses of HMB-002
- The VELORA Pioneer study continues enrollment and dose escalation in Part A, supporting development of HMB-002 as a prophylactic therapy for VWD

Abbreviations: FVIII, factor VIII; SQ, subcutaneous; VWD, von Willebrand disease; VWF, von Willebrand factor.
Full study details available at ClinicalTrials.gov (NCT06754852).

Acknowledgement

The authors thank the study participants, their families, the investigators and study site personnel

Authors: Priyanka Raheja[1], Olga Tsiamita[1], Amy Knott[2], Ulrike Lorch[3], Jigar Amin[4], Pruthvi Nagilla[4], Tara O'Meara[4], Shivangi Mathy[4], Henrik Ostergaard[4], Benny Sorensen[4], Catherine Rea[4]

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HMB-002 Evidence @ ISTH

3 Oral Presentations
(LB 01.4, OC 08.4, OC 59.5)

1 Poster Presentations
(PB1373)

NOW ENROLLING

VELORA Discover

Observational prospective screening study of bleeding and treatment in VWD Type 1 *(NCT06610201)*

VELORA Pioneer

Phase 1/2 study of HMB-002 to prevent & reduce the frequency of bleeding in VWD Type 1 *(NCT06754852)*

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