VELORA Pioneer: First-in-human investigation of HMB-002: a subcutaneous antibody for prophylactic management of Von Willebrand disease

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Conflicts of Interests

Disclosures for Dr. Raheja:

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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

Importance of Von Willebrand Factor (VWF)

Facilitates Hemostasis

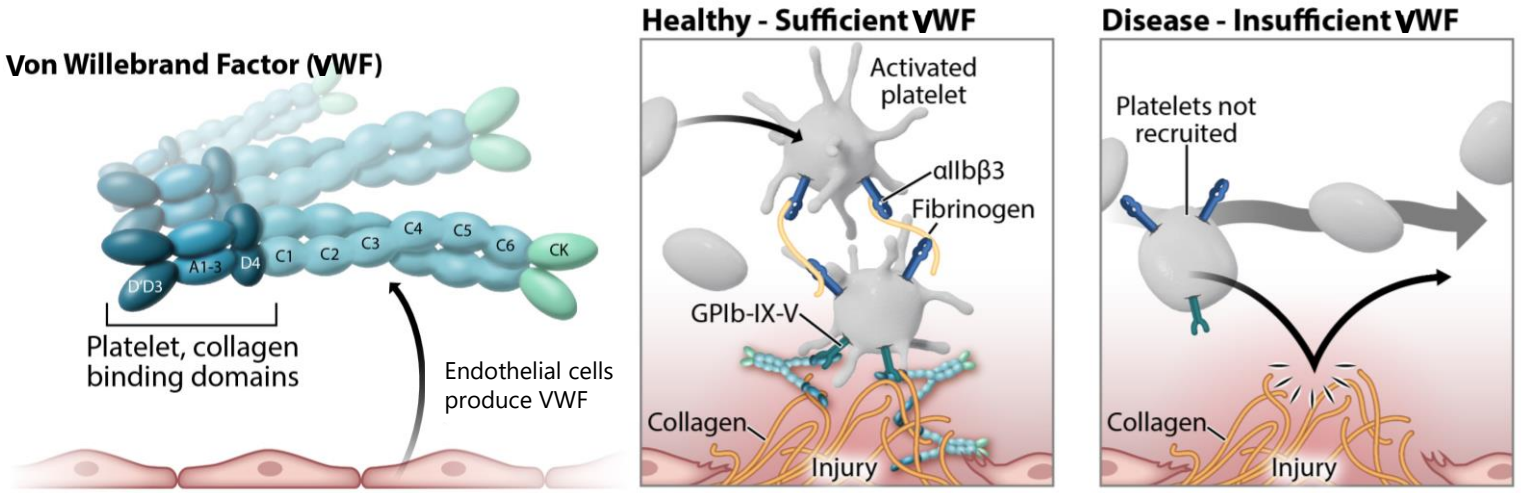
Mediates platelet adhesion at sites of vascular injury by binding exposed collagen and platelet receptors. Initiates **primary hemostasis,** enabling platelet activation and aggregation

Supports Factor VIII

Serves to carry and protect FVIII protein, safeguarding it from proteolytic degradation, to support **secondary hemostasis.**

Novel Functions

Interacts with over 60 molecular or cellular targets. Influences diverse cell types.



Von Willebrand disease (VWD) arises from a quantitative deficiency or defect in Von Willebrand factor (VWF), leading to impaired primary and secondary hemostasis

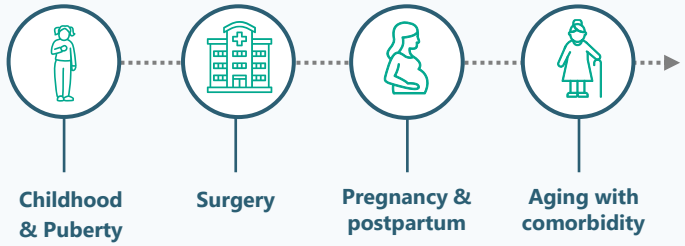
References: Ruggeri ZM, Mendolicchio GL. Interaction of von Willebrand factor with platelets and the vessel wall. Hamostaseologie. 2015;35(3):211-24. Sang Y, Roest M, de Laat B, de Groot PG, Huskens D. Interplay between platelets and coagulation. Blood Rev. 2021 Mar;46:100733.

Von Willebrand Disease (VWD)
A lifelong disorder with diverse, under-served needs

A diverse, under-recognized population

- The most common inherited bleeding disorder affecting 1% of the population.
  - Type 1: ~70-80%
  - Type 2A: ~20%
- The disorder affects both sexes.

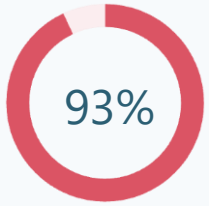
A lifelong continuum of need:



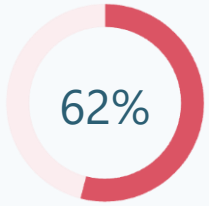
Burden of bleeding

- A median of **4 untreated bleeds per month** (range: 0–58), suggesting that bleeding may be normalized, under-reported, or undertreated.
- A sustained psychosocial toll: fear of bleeding, low mood, and social and relationship impact.
- **86%** of affected women say bleeding harms daily life, school, or work.

Hidden Burden



of women with VWD report **prolonged and heavy menstrual bleeding** [1]



of menstruating women have **iron deficiency,** even while on current treatment[1]

Gaps in current management

- Care is largely **reactive** — focused on treating bleeds rather than preventing them.
- Recognized limitations of standard options include tachyphylaxis, the burden of IV administration, and unsuitability for some older or comorbid patients.
- Higher VWF levels are associated with **lower bleed scores and reduced severity.**[3–6]

Limited evidence-based prophylaxis options

Disease	Treatment Option	Period
Hemophilia	On-demand facility based	1960s–1970s
	On-demand homecare	1970s–1980s
	Prophylaxis era	1970s–2000s
	Personalized prophylaxis	1970s–2000s
	Non-factor prophylaxis/therapy	2017–present
	Gene therapy	2020s
VWD	On-demand treatment era	1960s–2015
	Limited prophylaxis era	2015–2025
	Still waiting...	2025+

An unmet need remains for prophylactic options that address the underlying cause of VWD

References: 1. Khair K, et al. ISTH Congress 2025. Poster PB1432 & PB1460 (VWD 360 Study). 2. Myrin-Westesson L, et al. Res Pract Thromb Haemost. 2025 3. Sadler JE, et al. Hematology Am Soc Hematol Educ Program. 2009. 4. Tosetto A, et al. J Thromb Haemost. 2006. 5. Sadler JE, et al. Blood. 2003. 6. Federici AB, et al. Blood. 2014. Abbreviations: IV, intravenous; SC, subcutaneous; VWD, von Willebrand disease; VWF, von Willebrand factor.

HMB-002: Monoclonal Antibody to VWF Designed to Increase VWF and FVIII

HMB-002 Designed to:

Accumulate VWF to restore hemostasis in VWD

- Rescues VWF from degradation through engagement of the FcRn recycling pathway[1]
- *Primary Hemostasis*: Elevated VWF enhances platelet recruitment
- *Secondary Hemostasis*: Elevated VWF levels drive accumulation of FVIII and support thrombin generation & clot formation

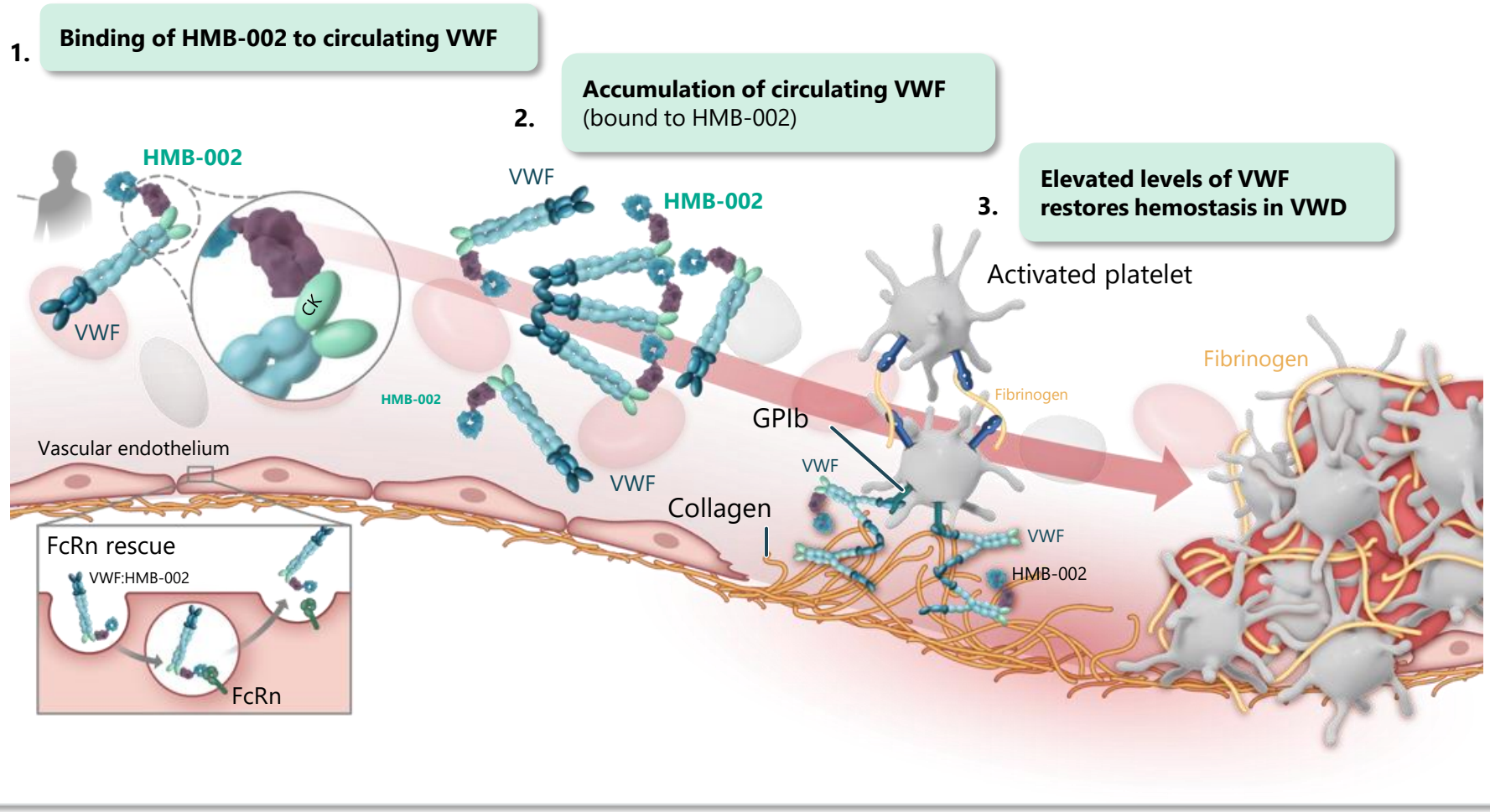
Preserve Regulation

- Maintains ADAMTS13-mediated VWF processing

Clinically validated therapeutic hypothesis

- Increasing endogenous VWF is clinically validated by 50 years of DDAVP use

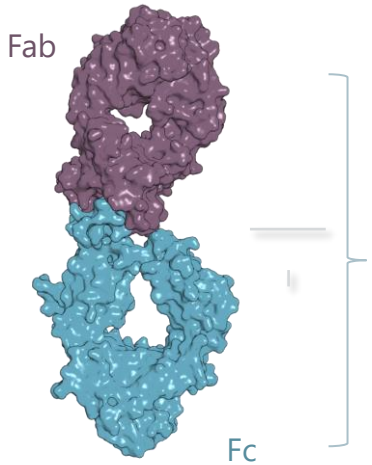
Mechanism of Action



References: 1. Häger M, et al. ISTH 2025. Oral OC 08.4. 2. Häger, Mattias, et al. "HMB-002: A Monovalent Antibody that Elevates Circulating VWF and FVIII Levels for Treatment of Von Willebrand Disease." Blood Advances (2026).
Abbreviations: VWD, Von Willebrand Disease; VWF, von Willebrand factor.

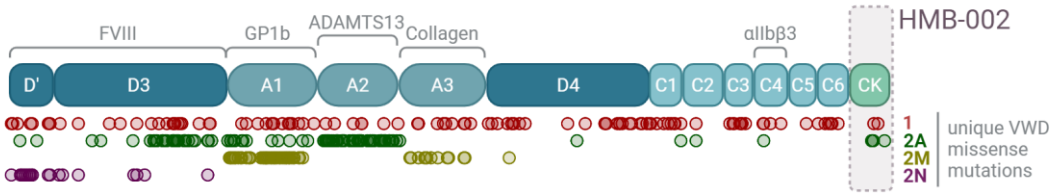
HMB-002: Rational Design of Antibody to Address Root Cause of VWD

Design Rationale[1,2]



HMB-002

1. **Monovalent design**
   - Prevents VWF crosslinking
   - Native multimer distribution preserved in vivo
2. **Strategic Binding Site**
   - Away from key functional sites (CK domain)
   - Few disease-causing mutations in the CK domain



Monitoring & Administration

1. **Monitored with Standard Assays**
   - VWF Retains key functions in presence of HMB-002

VWF:Ag	VWF:GPIb
VWF:RCo	FVIII

2. **Subcutaneous injection**
   - Fixed, low-volume dosing
   - Infrequent dosing enables prophylaxis

References: 1. Häger M, et al. ISTH 2025. Oral OC 08.4; 2. Rasmussen C, et al. ISTH 2025. Oral OC 59.5. Abbreviations: VWD, Von Willebrand disease; VWF, von Willebrand factor.

VELORA Program Overview

Now Enrolling

VELORA Discover

PROSPECTIVE, NATURAL HISTORY STUDY
(N=100+)

Large prospective natural history study capturing real-world bleeding burden and quality of life in patients with VWD.

Patient progression

Now Enrolling

VELORA Pioneer

PHASE 1 / 2 CLINICAL STUDY

- **VELORA Pioneer** is a three-part protocol
  - **Part A:** evaluate PK, PD, and safety of HMB-002 following a single fixed SC dose
  - **Part B:** evaluate PK, PD, and exploratory efficacy following multiple SC doses
  - **Part C:** evaluate single dose HMB-002 with concomitant IV factor concentrate

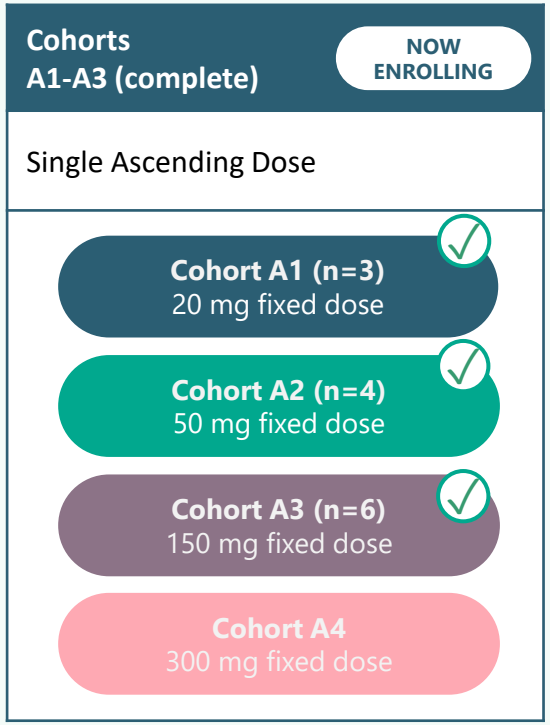
KEY INCLUSION CRITERIA:
- Type 1 VWD (including Type 1C), Type 2A, and Type 3 (Part C only)
- VWF activity ≤50% at baseline | FVIII activity ≤70% at baseline
- Males and females | Age 18 to 65 years
- Minimum 3 treated bleeds per year
- Oral contraception containing estrogen allowed

Presenting data from the first 3 cohorts of the Part A, single ascending dose study (Cohorts A1-A3)

Abbreviations: IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous; VWD, Von Willebrand disease.
Full eligibility criteria available at ClinicalTrials.gov (NCT06754852). Interim data cutoff as of 07 May 2026.

VELORA Pioneer: Phase 1/2 Study of HMB-002 in Individuals with VWD

Baseline Demographics and Disease Characteristics



	Cohort A1 20 mg (n=3)	Cohort A2 50 mg (n=4)	Cohort A3 150 mg (n = 6)	Total (n=13)
Demographics				
Age (yr), mean (range)	39 (27 – 62)	30 (21 – 53)	37 (20 – 54)	35 (20 – 62)
Sex, n (%)				
Female	1 (33)	3 (75)	3 (50)	7 (54)
Male	2 (67)	1 (25)	3 (50)	6 (46)
Weight (kg), mean (range)	74 (62 – 88)	73 (70 – 78)	69 (54 – 80)	72 (54 – 88)
VWD Subtypes	Type 1: 3 (100)	Type 1: 4 (100)	Type 1: 4 (67) Type 1C: 2 (33)*	Type 1: 11 (85) Type 1C: 2 (15)*
Baseline Laboratory Values, (range)				
VWF:Ac (%)	24.2 (21.1 – 26.0)	19.2 (9.5 – 36.0)	18.4 (7.3 – 29.4)	19.9 (7.3 – 36.0)
VWF:Ag (%)	23.6 (23.0 – 23.9)	22.4 (12.8 – 39.8)	16.9 (8.4 – 30.2)	20.2 (8.4 – 39.8)
FVIII:C (%)	43.7 (42.1 – 46.8)	38.9 (17.2 – 60.1)	29.8 (4.8 – 63.1)	35.8 (4.8 – 63.1)

*A total of 3 participants have Type 1C VWD; one participant was reclassified as Type 1C in the clinical database following the data cut.
Abbreviations: FVIII:C, factor VIII coagulant activity; VWD, Von Willebrand Disease; VWF:Ac, Von Willebrand Factor activity; VWF:Ag, Von Willebrand Factor antigen
Full eligibility criteria available at ClinicalTrials.gov (NCT06754852). Interim data cutoff as of 07 May 2026.

Interim Safety Summary

The emerging safety data for HMB-002 remained favorable across all cohorts studied [a]

- One participant experienced a Grade 1 increase in fibrin D-dimer, considered secondary to strenuous physical activity and unrelated to HMB-002

Key Findings

- **Most TEAEs were mild to moderate in severity and resolved**
- **No serious TEAEs**
- **No TEAEs considered related to HMB-002**
- **No discontinuations due to TEAE**
- **No thromboembolic events, injection site reactions, thrombocytopenia, or hypersensitivity**
- **No trends in inflammatory markers or vital signs**
- **Transient ADA increase in one Cohort A3 participant; no safety or PK/PD impact**

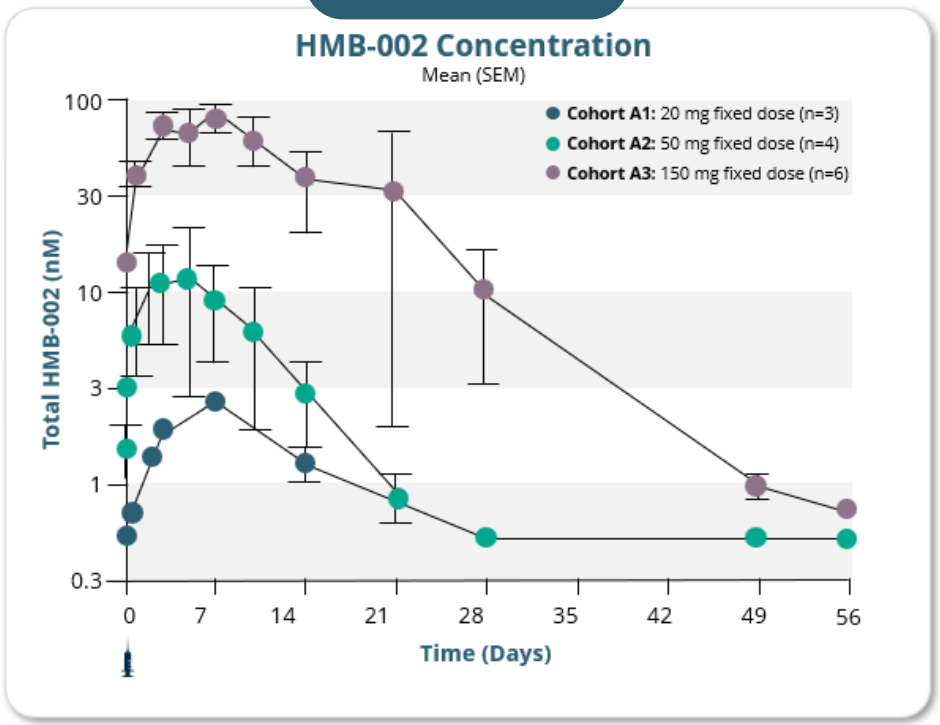
Category	N=13 [b] n (%)
All TEAEs	7 (53.8%) [c]
≥ Grade 3 TEAEs	1 (7.7%)
Serious TEAEs	0 (0%)
TEAEs leading to discontinuation	0 (0%)

Cohort	#TEAEs
A1	0
A2	7
A3	5

[a] Cohort A1 and Cohort A2 completed (56-days follow-up) and Cohort A3 on study (28-72 days follow-up); [b] N = number of participants and (%) = number of participants/N*100; [c] If a participant experienced more than on TEAE, the participant is counted once at the most severe or most related event.
Abbreviations: ADA, anti-drug antibody; PD, pharmacodynamics; PK, pharmacokinetics; SAE, serious adverse event; TEAE, treatment-emergent adverse event. Interim data cutoff of 07 May 2026.

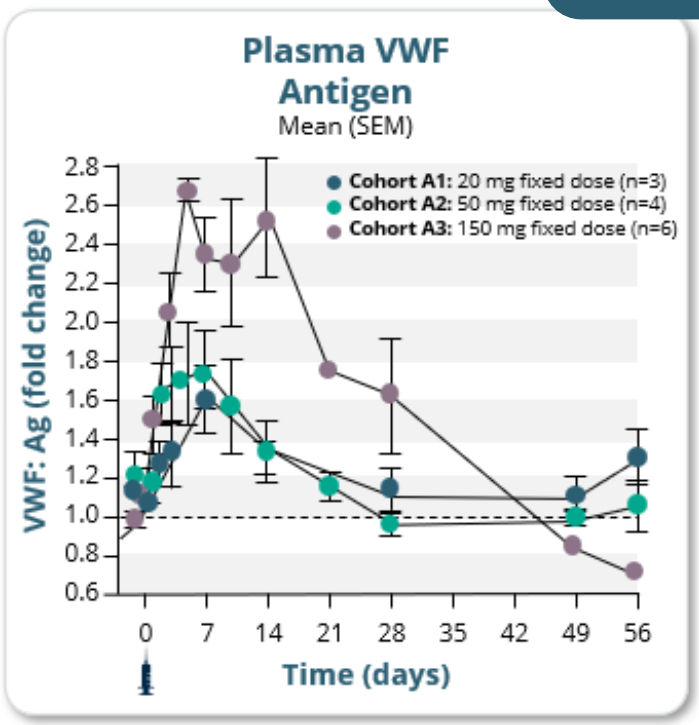
Dose-dependent Increase in PK Achieved >2-Fold Peak Elevation in PD Markers

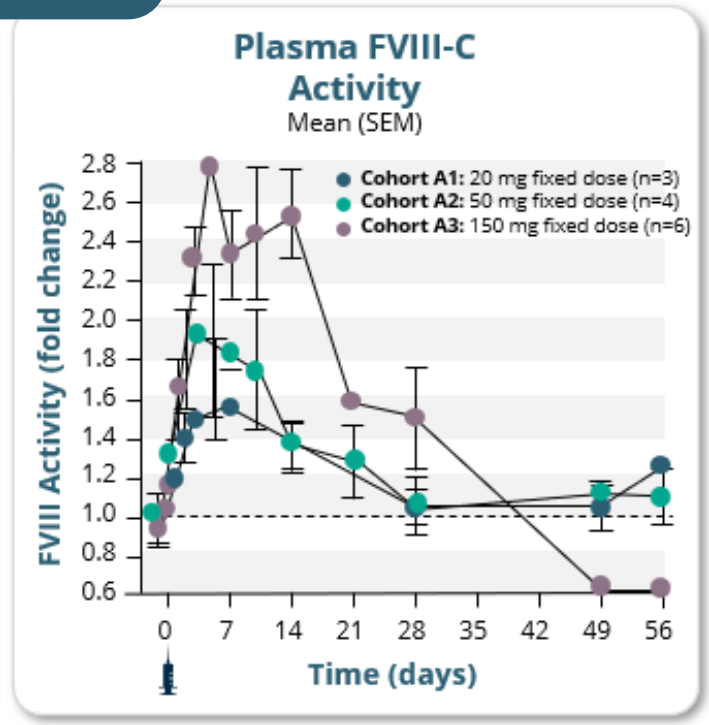
PK



- Observed a dose-dependent increase in C_{max}
- T_{max} was observed between Day 6-9
- Cohort A3 (150 mg) maintained detectable levels out to Day 56, suggesting extended duration potential

PD





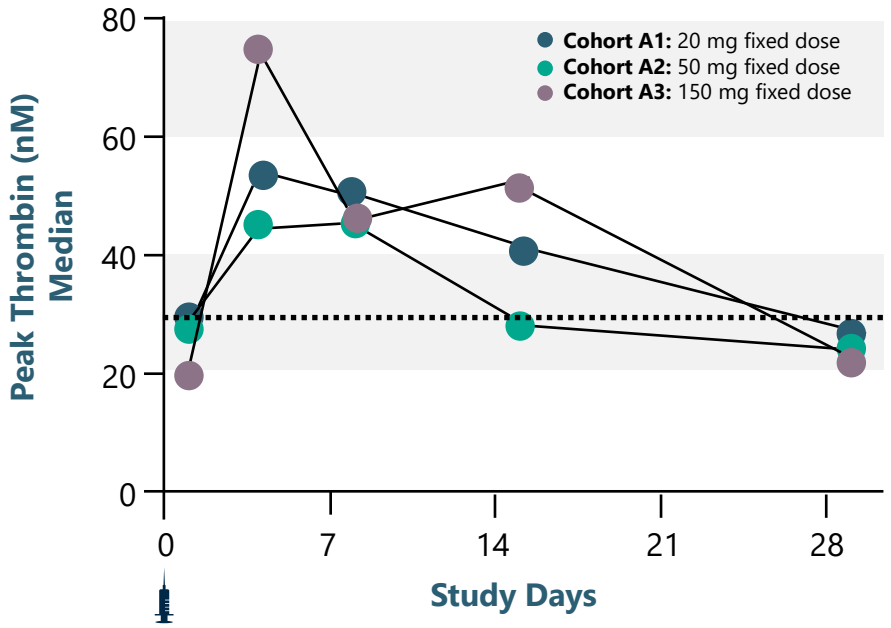
- Dose-related increases in VWF antigen and FVIII activity were observed following HMB-002 administration
- Higher dose levels were associated with greater and more sustained PD responses
- ≥2.4-fold VWF antigen and FVIII activity at 150 mg dose
- At all doses, VWF and FVIII activity remained within protocol defined upper limit of normal (<200 IU/dL)
- Multimer distribution remained stable through Day 29 across all dose levels

Abbreviations: C_{max}, maximum concentration; FVIII:C, factor VIII coagulant activity; VWD, Von Willebrand Disease; VWF, Von Willebrand factor; VWF:Ag; PD, pharmacodynamics; SEM, standard error of the mean; Tmax, time to maximum concentration.

Parallel Normalization of TG and APTT Correction Consistent with FVIII Accumulation

Thrombin Generation

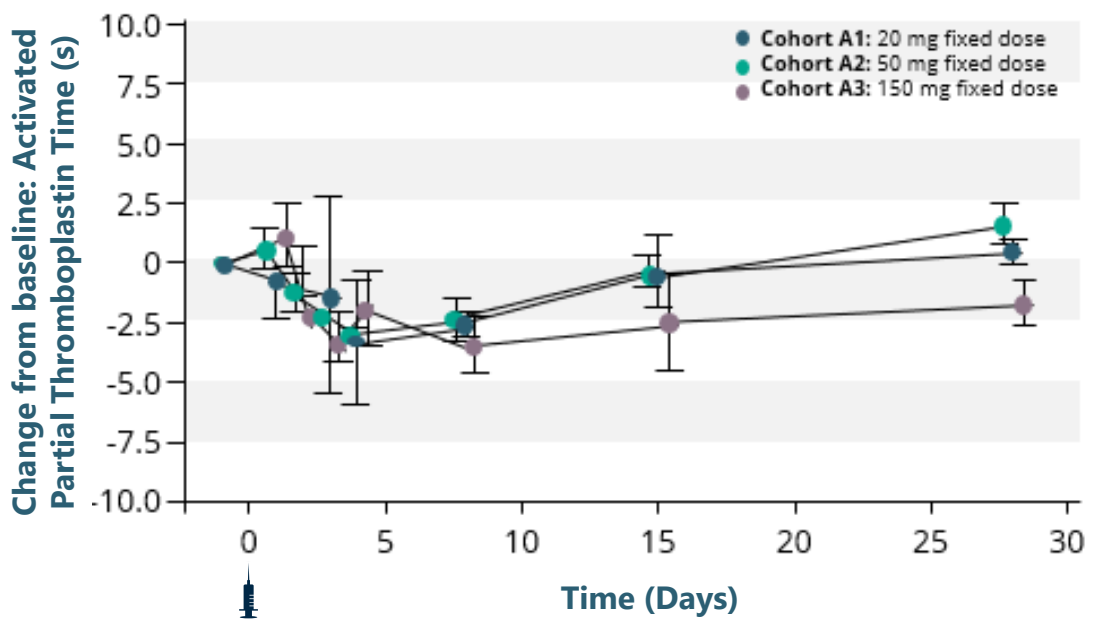
Median Peak Thrombin Levels (nM)



Thrombin generation was elevated to within normal range in all cohorts (reference range: 29.0 – 172.7 nM)

APTT Improvement

Median Peak Thrombin Levels (nM)



Improvement of APTT as measured by standard assays observed across all cohorts

Abbreviations: APTT, activated partial thromboplastin time; FVIII, factor VIII; SEM, standard error of the mean; TG, thrombin generation.
Methods: Calibrated Automated Thrombography, 0.5 pM tissue factor, platelet-poor plasma.
Note: Exploratory endpoint in Phase 1 (n=2, 4 and 5 evaluable in Cohorts A1, A2, and A3, respectively; two participants excluded due to baseline interference, reference interval in healthy donors: 29.0 – 172.7 nM thrombin).

Preliminary Clinical Observations

	Velora Discover Baseline ATBR N=10 [a]	Velora Pioneer Post HMB-002 ATBR N=9 [b]
Mean	20.1	1.6
Median	5.8	0.0
Range	0.0 – 101.5	0.0 – 14.6 [c]

Velora Discover: number of evaluable days, mean (range): 97.3 (7 – 166)
Velora Pioneer: number of evaluable days, mean (range): 22.7 (22 – 25)

- **Prospectively collected bleed data before HMB-002**
  - 2 out of 10 of participants had zero treated bleeding events on Velora Discover during the up to ~5.5 months observation period
- **Prospectively collected bleed data post HMB-002**
  - 8 out of 9 of participants experienced zero treated bleeding events on Velora Pioneer in the 28-day observation period [d] following a single dose of HMB-002

[a] Bleed diary data unavailable for 3 participants; Velora Discover participation is not required for enrollment on Pioneer Part A.
[b] Bleed diary data unavailable for 4 participants; diary completion was optional in Cohorts A1 and A2.
[c] One treated bleed was reported in 1 participant in Cohort A2 on Day 4.
[d] Velora Pioneer bleed analysis includes bleeds reported between Day 4-28 to reflect the pharmacological profile of HMB-002.
ATBR, annualized treated bleed rate is derived as the total number of treated bleeds/evaluable days (year) during Velora Discover or Pioneer study.
Evaluable days: days with a valid date entered in the bleed diary, regardless of the reported number of bleeds.
Analyses based on data cutoff of 04 May 2026; data are preliminary and subject to change following further review and cleaning of the ongoing clinical study database.

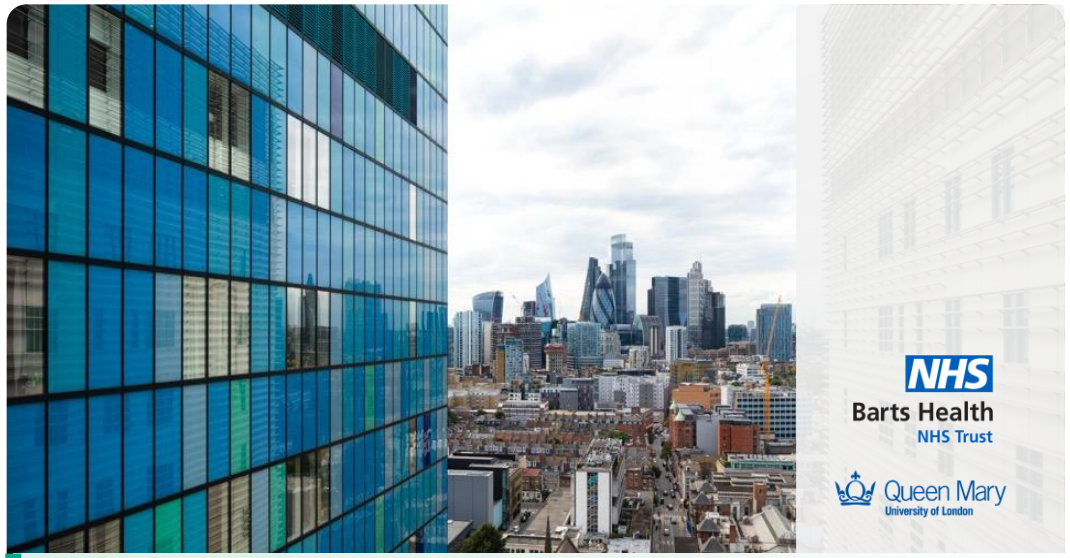
Summary and Conclusions

Conclusions

- HMB-002 has demonstrated proof of mechanism with dose dependent increases in PK and PD
- PD response can be monitored using standard assays, with greater than 2-fold peak VWF and FVIII observed
- Duration of PK and PD effect support the potential for monthly dosing
- Favorable emerging safety data, with no related TEAE and no SAE, enables further escalation and initiation of Part B and C
- Thrombin generation was elevated to within normal range in all cohorts, corresponding with appropriate shortening of APTT
- 8 out of 9 participants with Type 1 VWD had no treated bleeding events in the 28-days following a single dose of HMB-002
- Cohort A4 (300 mg single dose), B1 (150 mg Q4W), and Part C (150 mg single dose with concomitant factor concentrates) are open for enrollment

Abbreviations: APTT, activated partial thromboplastin time, FVIII, factor VIII; PD, pharmacodynamics; PK: pharmacokinetics; TEAE, treatment-emergent adverse event; SAE, serious adverse event; VWD, Von Willebrand Disease; VWF, von Willebrand factor.
Full study details available at ClinicalTrials.gov (NCT06754852).

Acknowledgements



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Sponsor: Hemab Therapeutics

Now Enrolling

VELORA Discover

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

VELORA Pioneer

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

Current sites and expanding…

United Kingdom
- Richmond Pharmacology
- The Royal London Hospital, Barts Health NHS trust
- Basingstoke and North Hampshire Hospital
- University Hospital of Wales
- Queen Elizabeth Hospital Birmingham

United States
- Arkansas Children's Hospital
- Emory University Hospital
- Innovative Hematology (Indiana)
- Mayo Clinic - Rochester
- Oregon Health & Science University
- Phoenix Children's Hospital
- Tulane University School of Medicine
- University of Miami Hospital
- University of Michigan Hospitals
- University of Texas Southwestern Medical
- Washington Center for Bleeding Disorders
- Children's Hospital of Los Angeles
- Hemophilia Center of Western Pennsylvania

Australia
- Fiona Stanley Hospital (Perth)
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