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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Conflicts of Interests

Disclosures for Dr. Raheja:

Shareholder	No relevant conflicts of interest to declare
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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

Importance of VWF

- Mediates **primary hemostasis**, through binding of collagen and platelets
- Mediates **secondary hemostasis** by carrying factor VIII
- VWD arises from a quantitative deficiency or defect in von Willebrand factor (VWF), a **protein essential for hemostasis**

Burden of VWD[1]

had **emergency department visits** for bleeding in past month

Women with VWD who report **prolonged and heavy menstrual bleeding**

Addressing the Root Cause

- Raising VWF ≥1.5 to 2x associated with decreased bleed scores and bleeding severity[2-5]
- Standard of care does not offer suitable prophylactic options for most patients

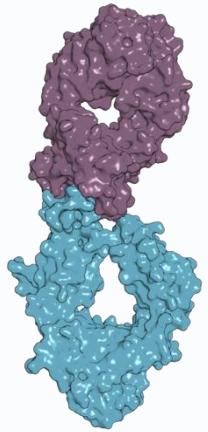
Treatment	Approved	Limitations
Nasal	1978	Limited by tachyphylaxis & short half-life
IV	1980s	Burden of multiple infusions per week
SC	-	None approved

Prophylactic subcutaneous treatment needed to address root cause of VWD

References: 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. Abbreviations: IV, intravenous; SC, subcutaneous.

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

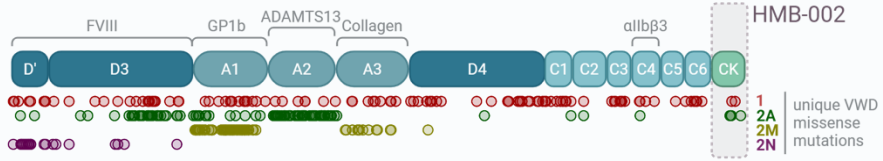
HMB-002



Design Rationale[1,2]

1. Binds at VWF CK domain

- Away from key active sites
- Few disease-causing mutations in the CK domain

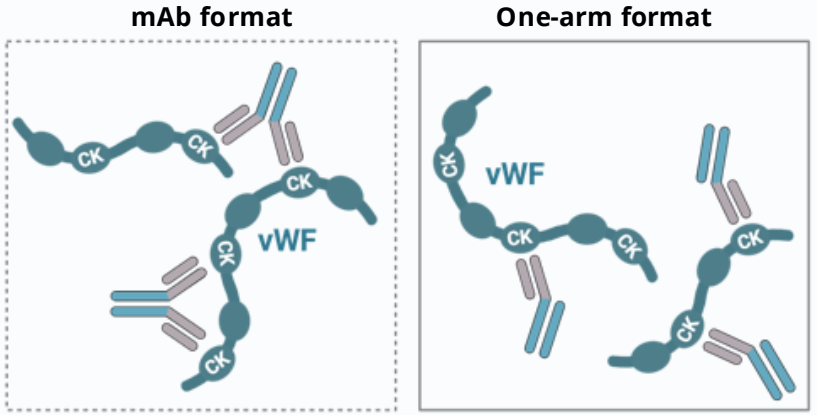


2. Monovalent antibody

- Monovalent design avoids VWF cross-linking
- Human IgG4 with Fc effector silencing

3. Subcutaneous injection

- Fixed, low-volume dosing
- Infrequent dosing enables prophylaxis



VWF Retains Key Functions in Presence of HMB-002

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.

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

HMB-002

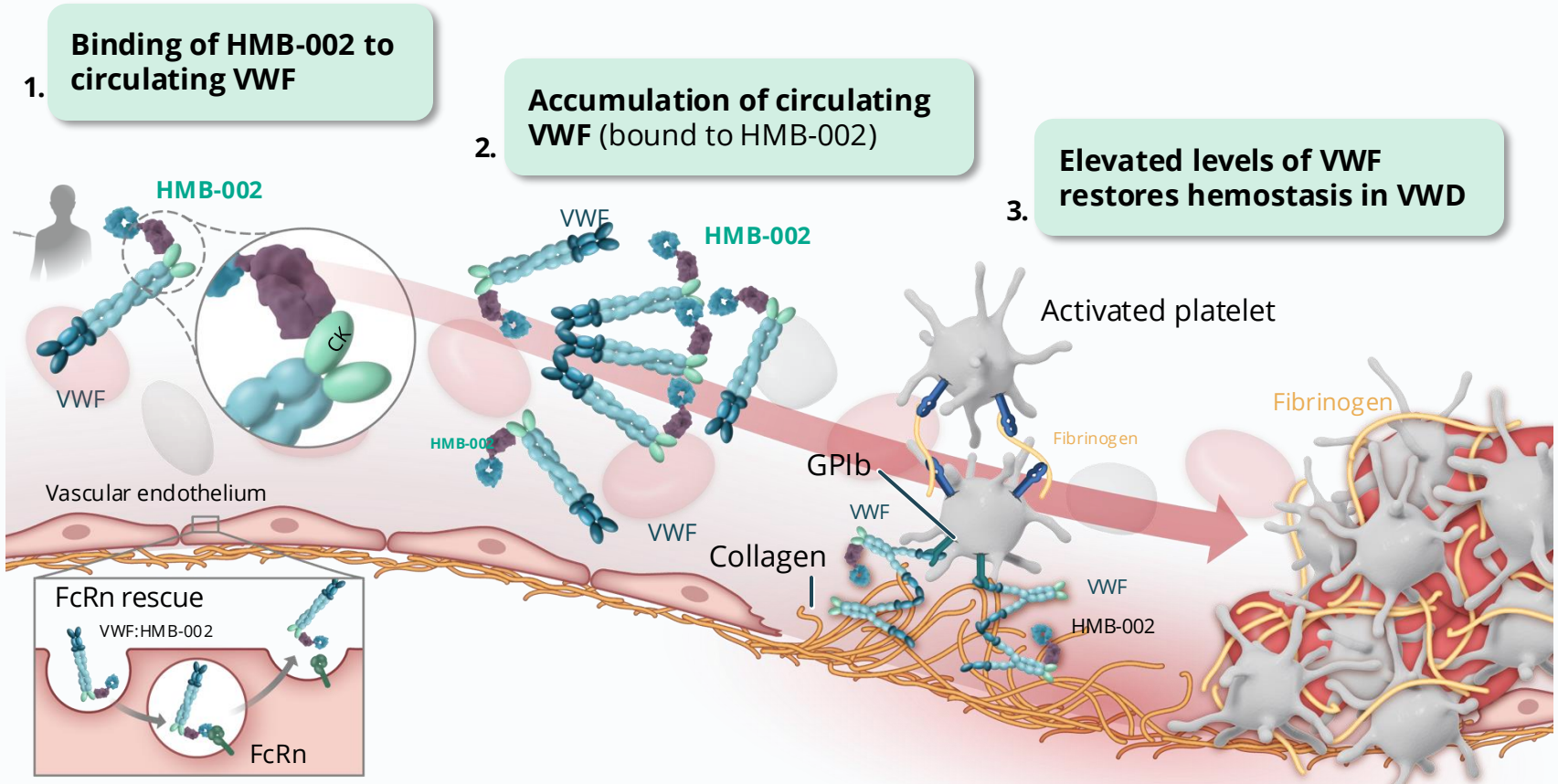
VWF accumulates and restores hemostasis in VWD

- Engages FcRn receptor and undergoes recycling via FcRn pathway, delaying clearance of VWF[1]
- *Primary Hemostasis*: Elevated VWF enhances platelet recruitment
- *Secondary Hemostasis*: Elevated VWF levels drive accumulation of FVIII and support thrombin generation & clot formation

Regulation Preserved

- ADAMTS13-mediated VWF processing maintained, ensuring safe multimer distribution

Mechanism of Action



References: 1. Häger M, et al. ISTH 2025. Oral OC 08.4. Abbreviations: VWD, Von Willebrand Disease; VWF, von Willebrand factor.

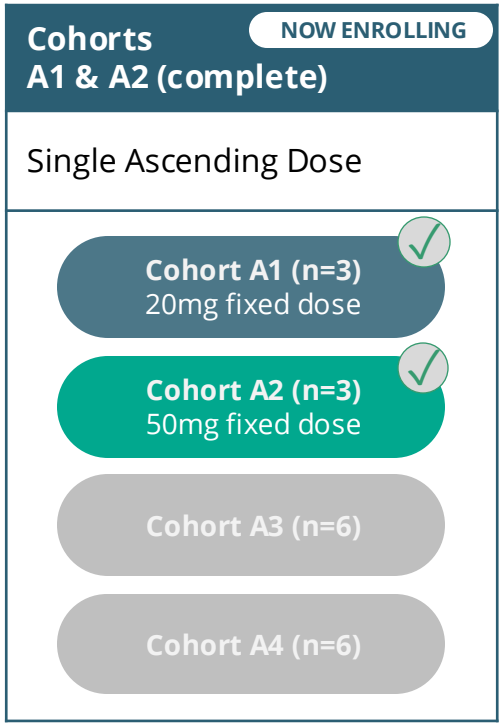
VELORA Pioneer: Phase 1/2 Study of HMB-002 in Individuals with VWD

Presenting data from the first 2 cohorts of the Part A, single ascending dose portion (Cohorts A1 and A2)

Velora Pioneer is a two-part protocol:
- Part A will evaluate PK, PD and safety of HMB-002 following a single fixed dose
- Part B will evaluate multiple doses

Key inclusion criteria in cohorts A1 & A2:
- Type 1 VWD
- VWF activity <40% at baseline
- FVIII activity <70% at baseline
- Males and females
- Age 18 to 65 years

Adaptive protocol design enabling future modifications to:
- Dose and dose regimen
- Duration of follow up to match the PD response



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

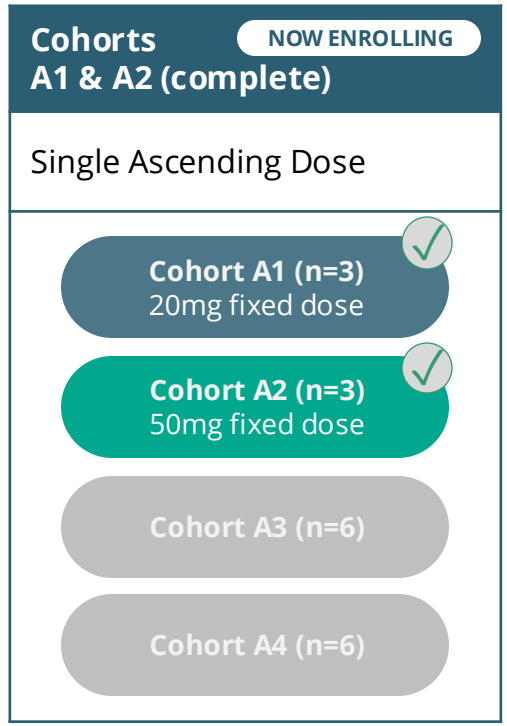
Baseline and Demographics

	Cohort A1 (n=3)	**Cohort A2** (n=3)	**Total** (n=6)
Demographics			
Age (yr), mean (range)	38.7 (27-62)	21.7 (21-22)	30.2 (21-62)
Sex, n (%)			
Female	1 (33.3)	2 (66.7)	3 (50.0)
Male	2 (66.7)	1 (33.3)	3 (50.0)
Race: White, n (%)	3 (100)	3 (100)	6 (100)
Weight (kg), mean (range)	73.53 (61.8- 87.6)	73.47 (70.0-77.7)	73.50 (61.8-87.6)
Baseline Laboratory Values, mean (range)			
VWF:Ac (%)	24.2 (21.1-26.0)	13.6 (9.5-20.4)	18.9 (9.5-26.0)
VWF:Ag (%)	23.6 (23.0-23.9)	16.6 (12.8-23.3)	20.1 (12.8-23.9)
FVIII:C (%)	43.7 (42.1-46.8)	33.5 (17.2-60.1)	38.6 (17.2-60.1)

Initial Safety Data: No Safety Concerns Identified

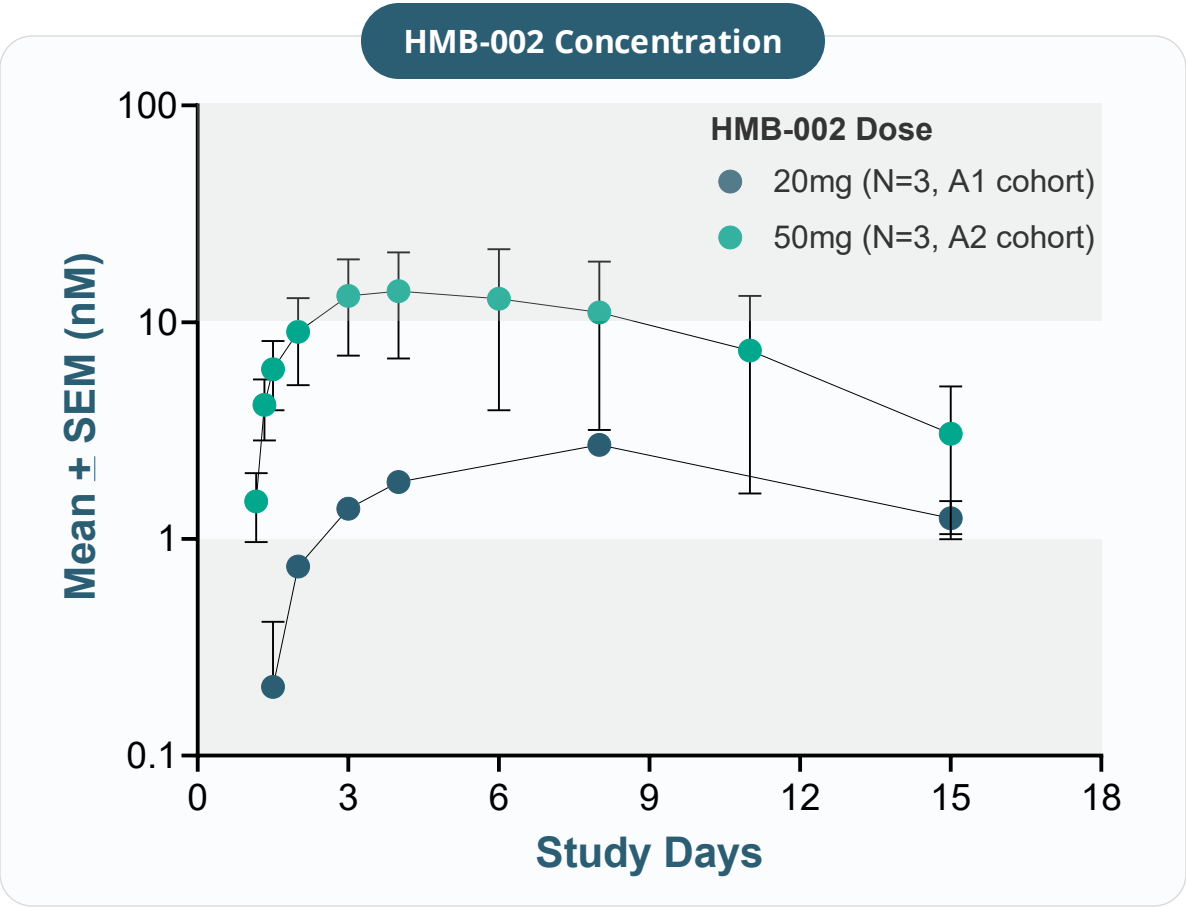
HMB-002 has demonstrated a favorable safety profile:

- Cohort A1 (20mg): No treatment-emergent adverse events (TEAEs) reported
- Cohort A2 (50mg): Two Grade 1 TEAEs observed, both assessed as unrelated
- 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)



Safety observation period:
A1 completed (56-days follow-up);
A2 ongoing (minimum 14 days follow-up presented)

Pharmacokinetics of HMB-002

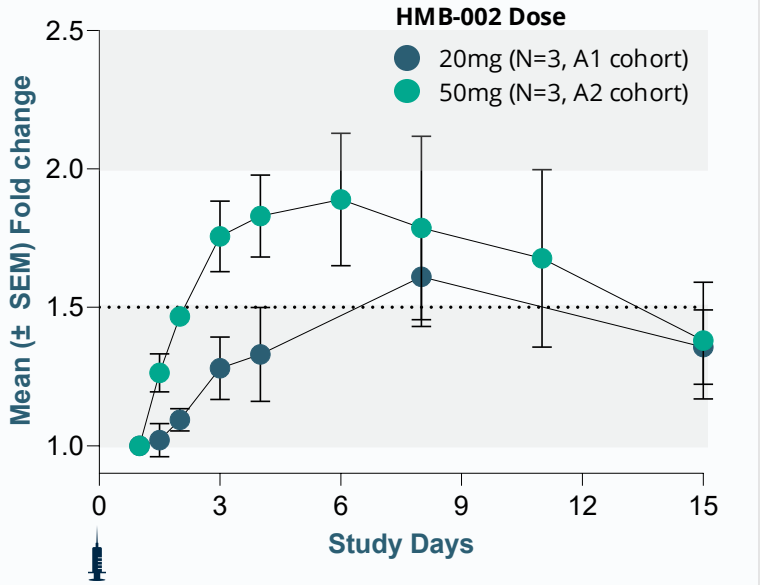


- Observed a dose-dependent increase in C_{max}
- T_{max} was observed earlier in A2 (50mg) cohort than in A1 (20mg) cohort
- A2 cohort (50mg) maintains higher plasma levels through to Day 15 of the study period, suggesting extended duration potential with increased doses of HMB-002

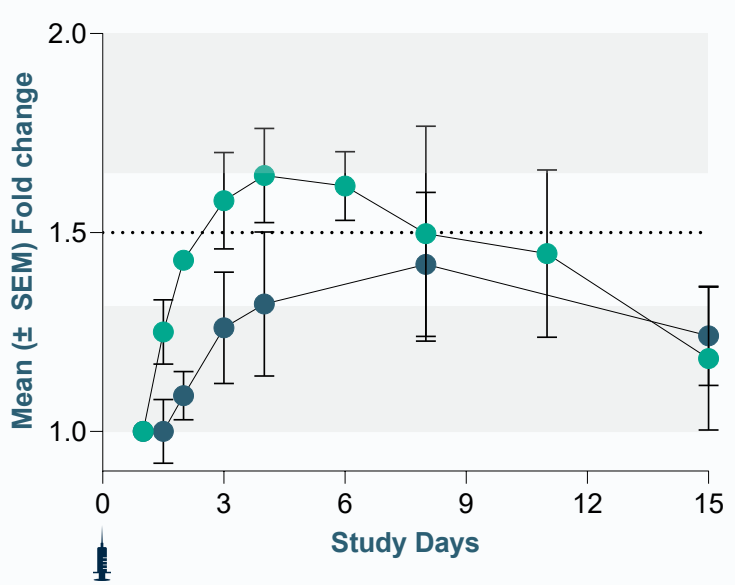
Abbreviations: PK, pharmacokinetics; SEM, standard error of the mean.

Pharmacodynamics of HMB-002

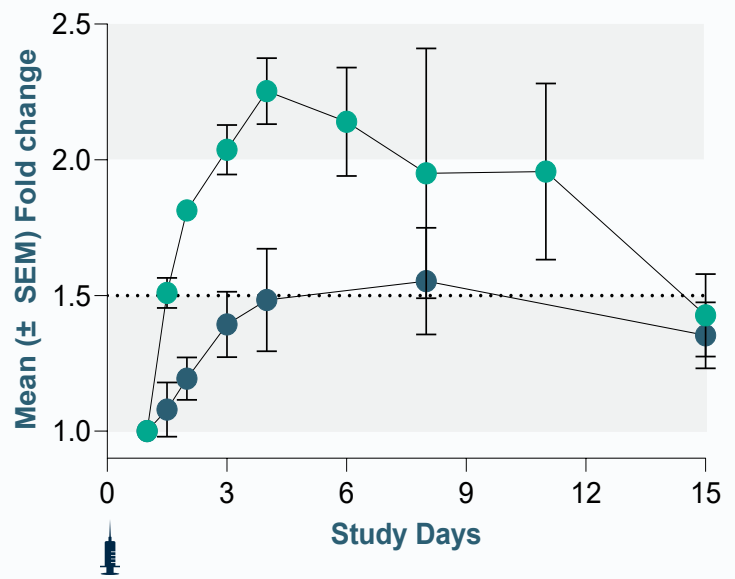
Plasma VWF Antigen



Plasma VWF Activity



Plasma FVIII-C Activity



*A2- 50mg last sample collected at day 15 at the time of data cut

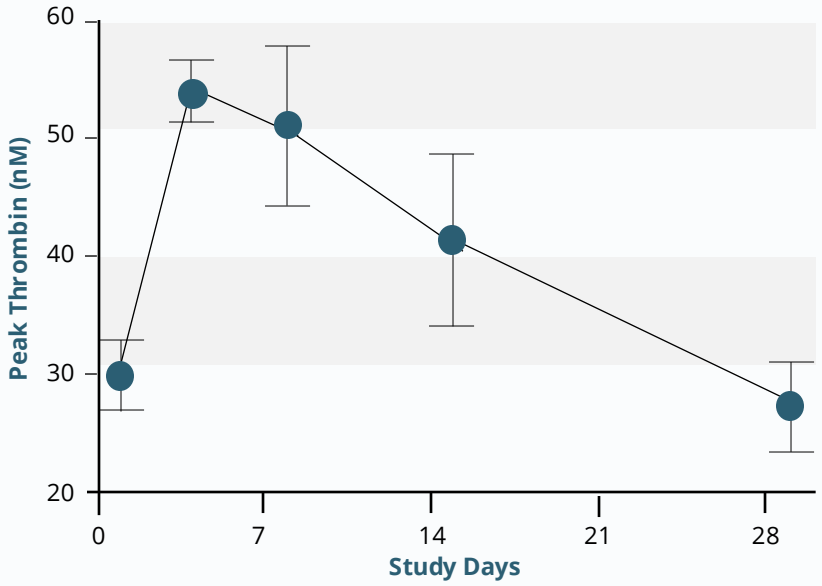
- Dose dependent increase and prolonged duration of accumulation of VWF antigen, VWF activity, and FVIII activity
- In the A2 cohort (50mg), >1.5-fold accumulation is observed for all three PD parameters, maintained for at least 8-10 days

Abbreviations: FVIII, factor VIII; PD, pharmacodynamics; SEM, standard error of the mean; VWD, Von Willebrand disease; VWF, von Willebrand factor.

Cohort A1: Improved Thrombin Generation and APTT with HMB-002

Thrombin Generation

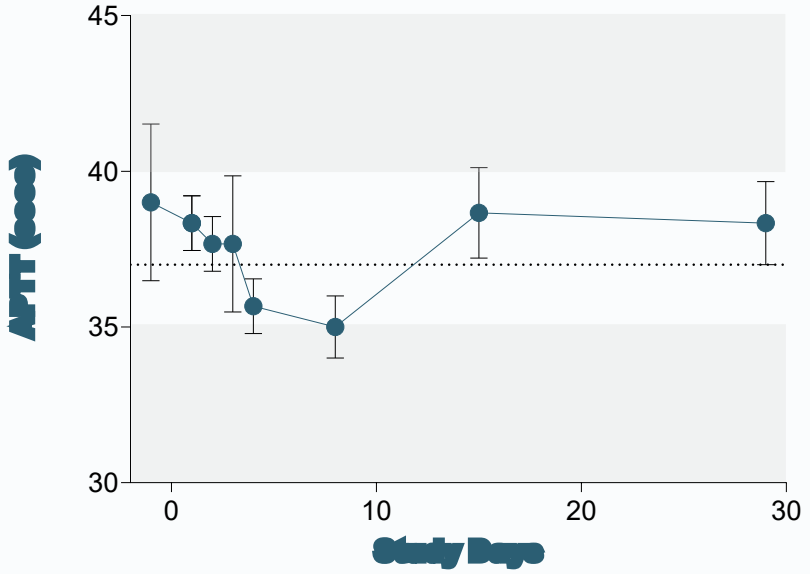
Mean (SEM) Peak Thrombin Levels (nM)



Peak TG correcting to levels equivalent to normal plasma (with approximately 55-65% FVIII*)

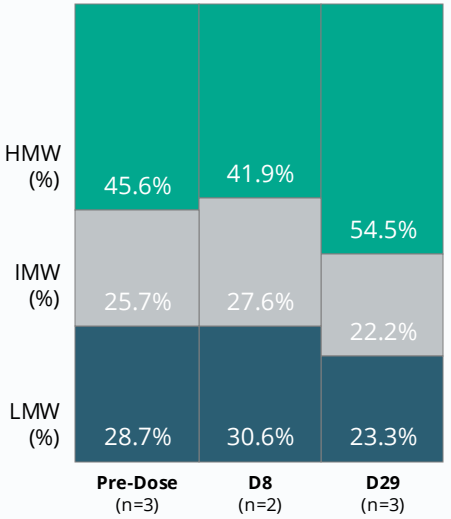
APTT Improvement

Mean (SEM) Activated Partial Thromboplastin



The coagulation effect of HMB-002 is measurable using standard APTT laboratory tests

Multimer Distribution



The multimer distribution remains stable^

Abbreviations: APTT, activated partial thromboplastin time; HWM, high-molecular weight multimers; IMW, intermediate-molecular weight multimers; LMW, low-molecular weight multimers; SEM, standard error of the mean; TG, thrombin generation. 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 endogenous thrombin potential.

Summary and Conclusions

HMB-002

- HMB-002 is a monovalent antibody designed to bind and accumulate endogenous circulating VWF and increase FVIII levels
- Elevation of native VWF and FVIII monitorable by standard assays
- Presented safety, PK and PD data from the first 2 cohorts in the single ascending dose portion of the study

Conclusions

- A dose dependent increase in PK and PD parameters has been observed
- With a dose of 50mg, >1.5-fold elevation VWF and FVIII has been achieved and this was maintained for at least 8-10 days
- No treatment-emergent adverse events have been recorded
- Safety and PK/PD 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; PD, pharmacodynamics; PK: pharmacokinetics; VWD, Von Willebrand Disease; VWF, von Willebrand factor. Full study details available at ClinicalTrials.gov (NCT06754852).

Next Steps

Key Inclusion Criteria:

- Confirmed Type 1 VWD (including Type 1C) with VWF levels <40%
- Regular bleeding events: 3 treated bleed events per year expected (Treated: DDAVP, TXA, Factor concentrate)
- Oral contraceptives allowed
- ≥16-18 and <65 years old*

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N = 55

VELORA Discover

Prospective,
natural history

NOW ENROLLING

VELORA Pioneer

Phase 1/2 Study
of HMB-002

*Full inclusion/exclusion criteria available at clinicaltrials.gov (VELORA Discover: NCT06610201; VELORA Pioneer: NCT06754852)
Abbreviations: DDAVP, desmopressin; TXA, tranexamic acid; VWD, von Willebrand Disease; VWF, von Willebrand Factor.

Acknowledgement

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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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