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Elevating Levels of Endogenous Circulating von Willebrand Factor (VWF): The Potential of HMB-002 as a Prophylactic Treatment of Von Willebrand Disease (VWD)

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Shareholder	Hemab Therapeutics
Grant / Research Support	No relevant conflicts of interest to declare
Consultant	No relevant conflicts of interest to declare
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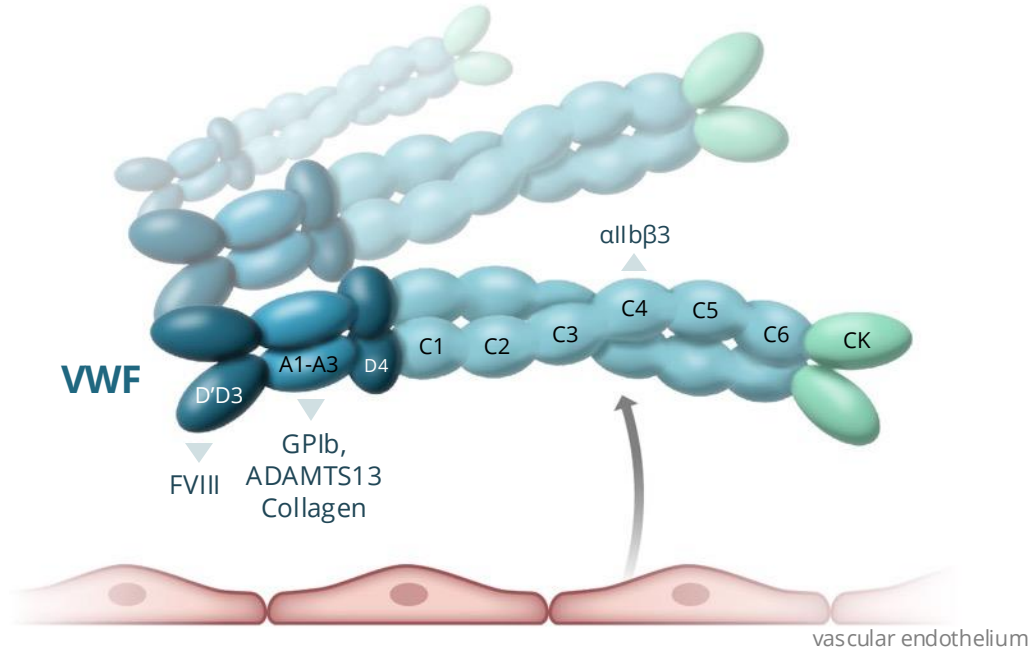
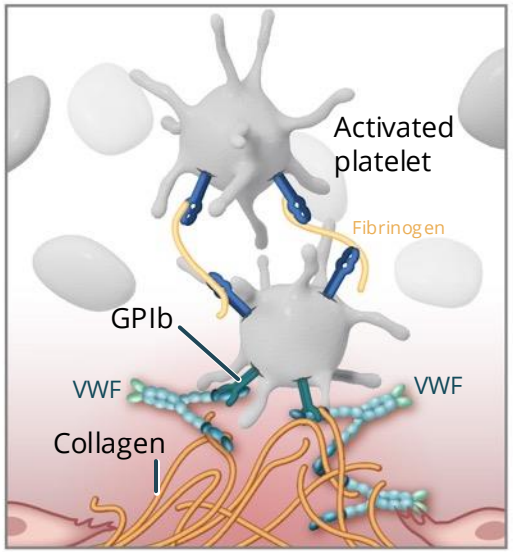
Speaker bureau	No relevant conflicts of interest to declare
Other	No relevant conflicts of interest to declare

Presentation includes discussion of the following off-label use of a drug or medical device: N/A

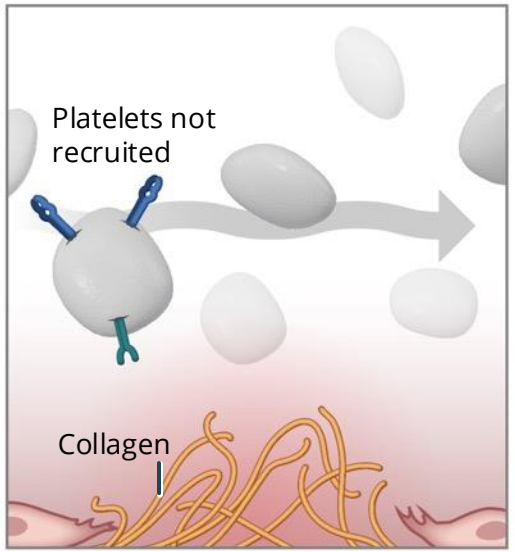
Von Willebrand Disease – A Bleeding Disorder with Unmet Needs



Healthy – sufficient VWF



VWD – insufficient VWF



Von Willebrand Factor (VWF)

- Multifunctional protein supporting
- **Primary hemostasis** by mediating platelet adhesion and aggregation at sites of vascular injury by binding exposed collagen and platelet receptors
- **Secondary hemostasis** by protecting FVIII in circulation

Von Willebrand Disease (VWD)

- Most common inherited bleeding disorder
- Results from **quantitative deficiency (0-50%) or defect in VWF**
- Broad spectrum of frequent bleeding events including heavy menstrual bleeding, often leading to iron deficiency

HMB-002 Aims to Directly Impact the Underlying Patho-etiology of VWD by Increasing Levels of VWF and FVIII

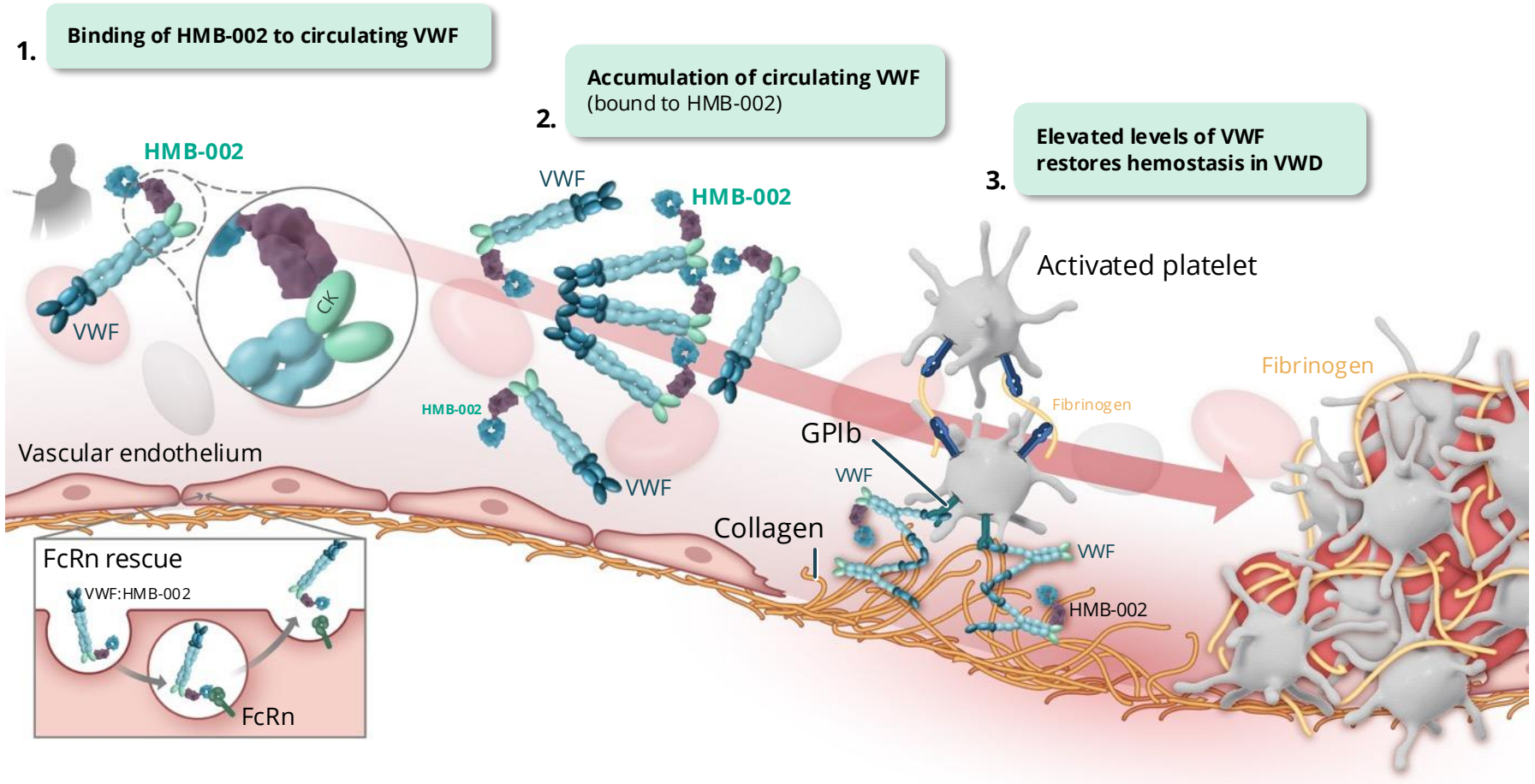
Functions of HMB-002

Binds & Accumulates VWF

- *Accumulates VWF*
  HMB-002 engages the FcRn pathway to protect VWF from degradation
- *Increases FVIII levels*
  Elevated VWF levels drive additional accumulation of FVIII

Restores Hemostasis in VWD

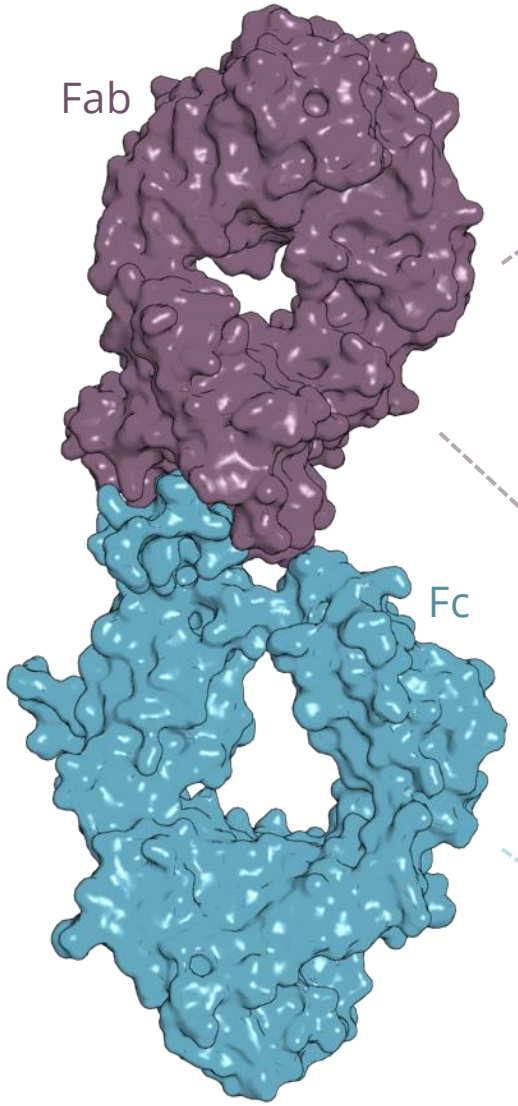
- *Primary Hemostasis*
  Elevated VWF levels enhance platelet recruitment to site of injury
- *Secondary Hemostasis*
  Accumulated FVIII further supports clot formation by contributing to secondary hemostasis



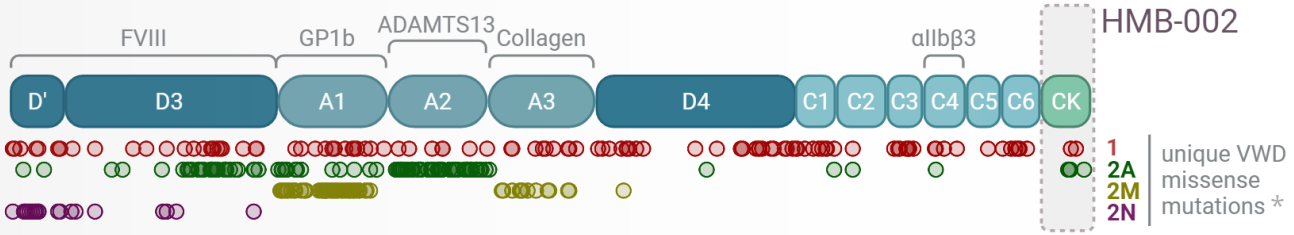
HMB-002 aims to offer subcutaneous, infrequent prophylactic treatment of people with VWD

References: Gandhi P, et al. Nat Cardiovasc Res. 2024; McCluskey G, et al. Haematologica. 2024.

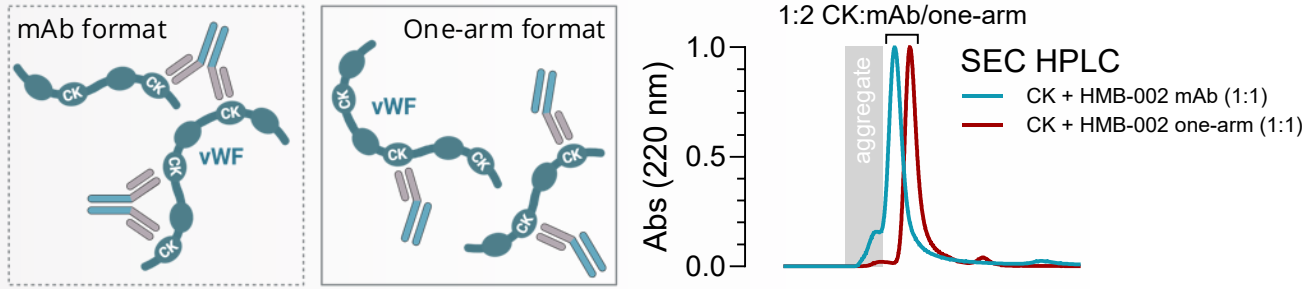
HMB-002 Designed to Bind the C-terminal CK Domain of VWF



Targeting the C-terminal CK domain in VWF



Monovalent (one-arm) human antibody format



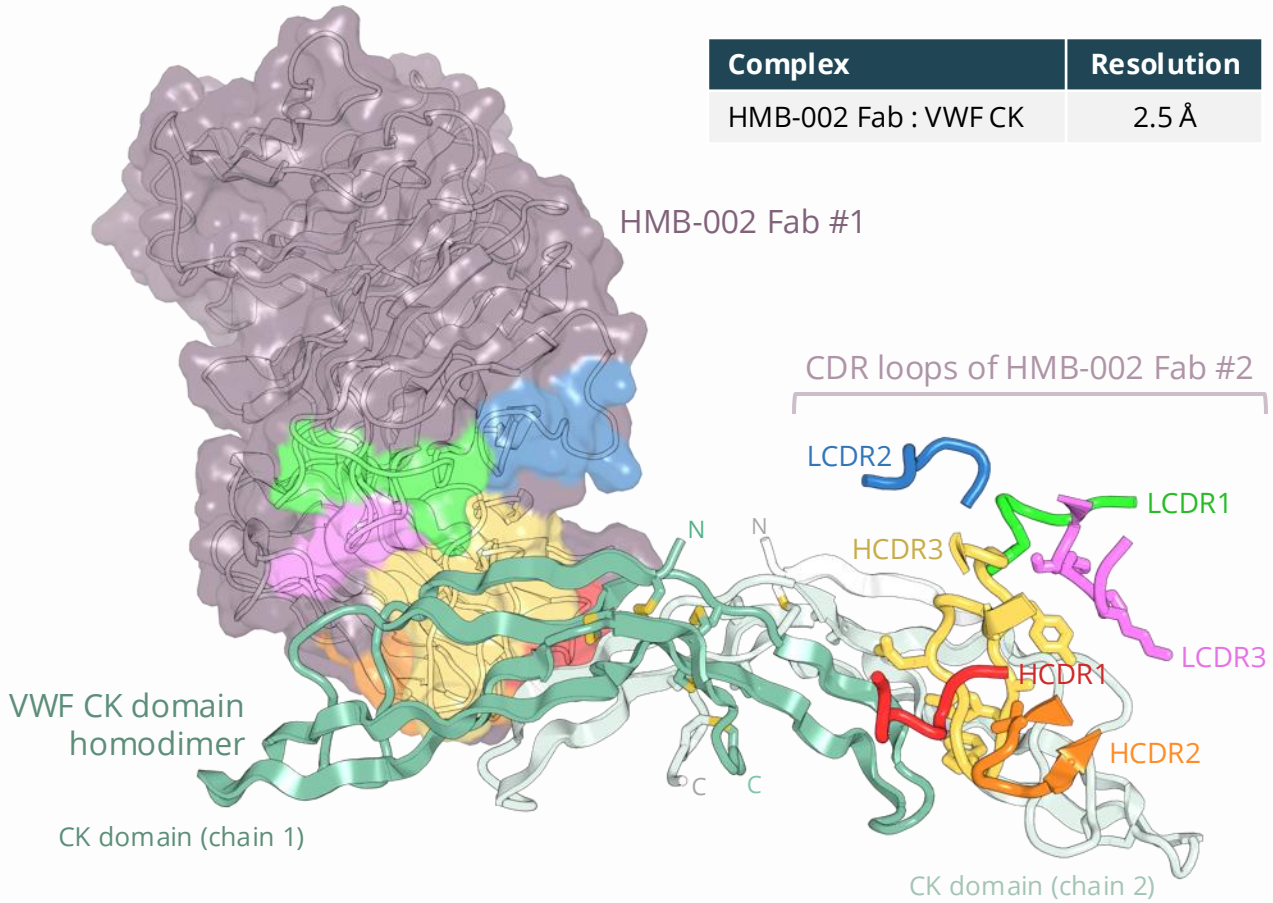
Human IgG4 + Fc effector silencing

- Significantly reduced Fcγ receptor binding compared to standard IgG4
- No cytokine release, platelet or completement activation in *ex vivo* studies[2]

References: 1. de Jong A, et al. Thromb Res. 2017;159:65; 2. Rasmussen C, et al. ISTH 2025 (Oral OC 59.5).

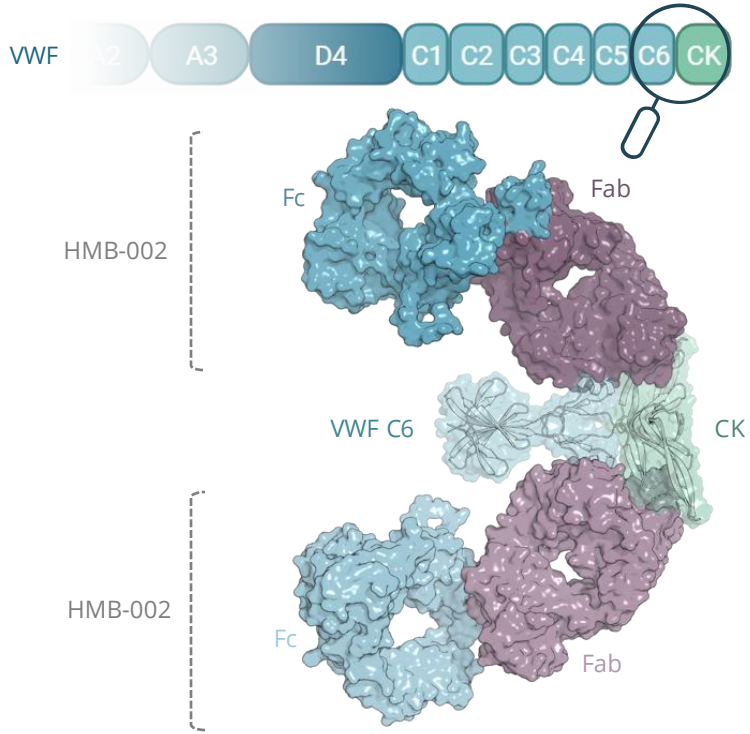
HMB-002 Selectively Binds to Epitope in the VWF CK Domain

Complex	Resolution
HMB-002 Fab : VWF CK	2.5 Å



No off-targets identified in screen of 6,500 human proteins using the Retrogenix® Cell Microarray Technology

Molecular model of full-length HMB-002 bound to the VWF C6-CK fragment*

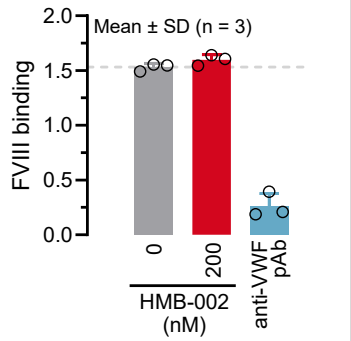


K_D for HMB-002 binding at pH 7.4 and 25°C (SPR)	VWF CK	Plasma-derived VWF
	0.6 nM	0.1 nM

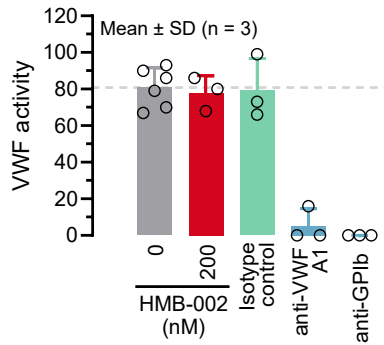
References: Chen X, et al. J Struct Biol. 2022; Zhou M, et al. Blood. 2014; Scapin G, et al. Nat Struct Mol Biol. 2015.

VWF Retains Key Functions in Presence of HMB-002

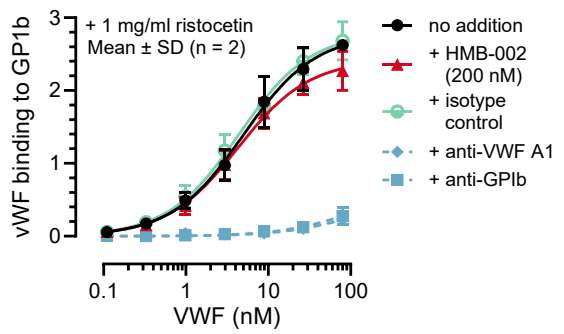
1 FVIII:VWF binding



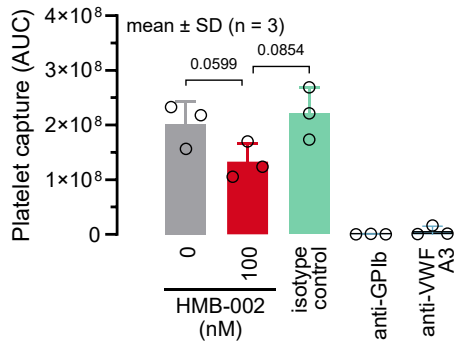
2 VWF:RCo activity

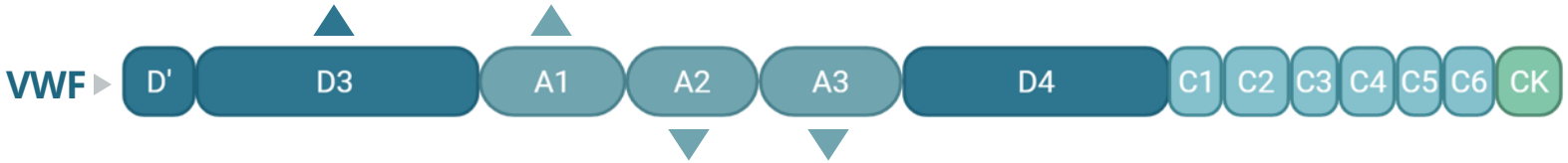


VWF:GP1b binding (ELISA)

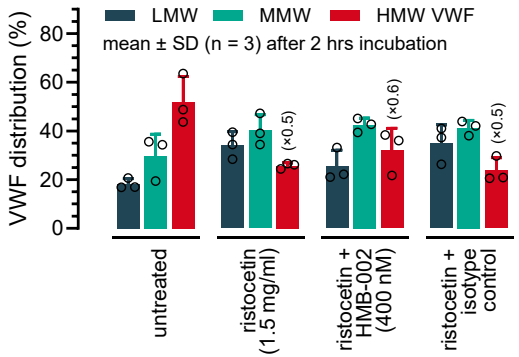


5 Whole-blood platelet capture on collagen surface at high shear

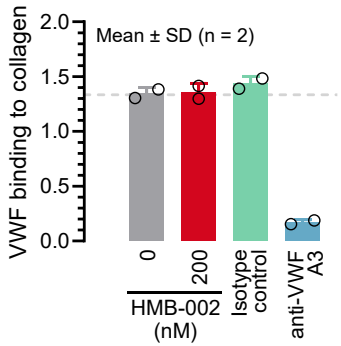




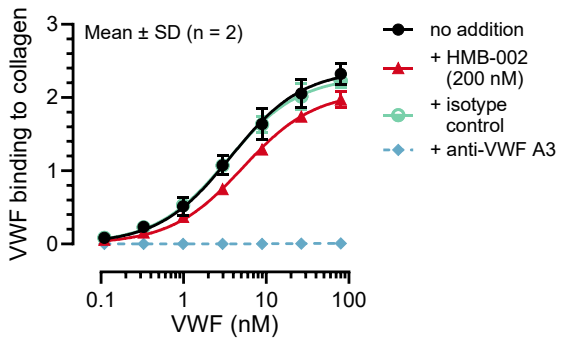
3 ADAMTS13 processing (plasma)



4 VWF:CBA



VWF:Collagen III binding (ELISA)

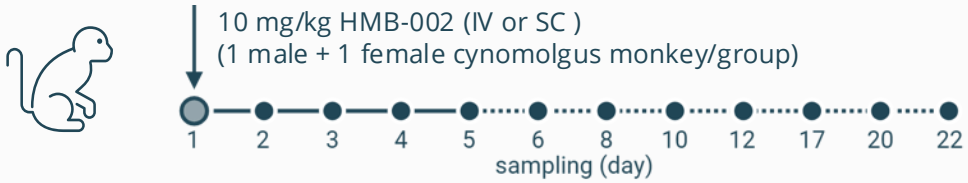


Methods

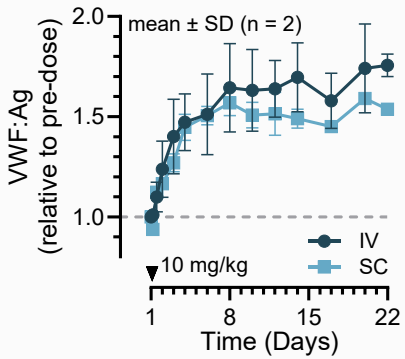
FVIII:VWF binding	Asserachrom® VWF:FVIIIB
VWF:RCo activity	STA®-VWF:RCo assay in citrated human plasma
VWF:GPIb binding	ELISA with immuno-captured GPIb ectodomain and ristocetin
ADAMTS13 processing	Citrated human plasma with ristocetin (2-h incubation)
VWF:CBA	ZYMUTEST™ VWF:CBA (collagen I/III)
VWF:Collagen ELISA	ELISA with coated human collagen III
Platelet capture at high shear	Microfluidic assay with citrated human whole blood and coated collagen I/III. Platelet capture recorded for 10 min at shear of 1000 s^{-1}

HMB-002 Accumulates Endogenous VWF and FVIII in Non-Human Primates

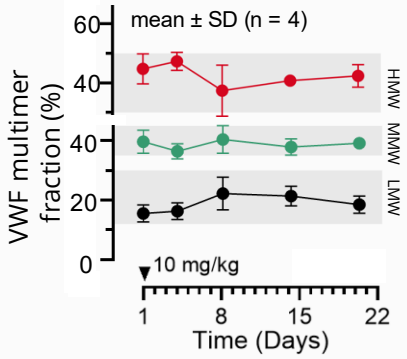
Prolonged VWF accumulation with retained multimer pattern after single-dose of HMB-002



VWF accumulation



VWF multimer distribution

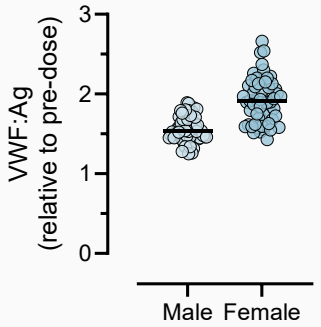


Assays

- VWF:Ag using ELISA and human plasma calibrator
- VWF:RCo using STA®-VWF:RCo (Stago) and human plasma calibrator
- FVIII:Ag using Asserachrom® FVIII:Ag (Stago) and human plasma calibrator
- VWF multimer by gel electrophoresis and immunostaining (Hydrasys)

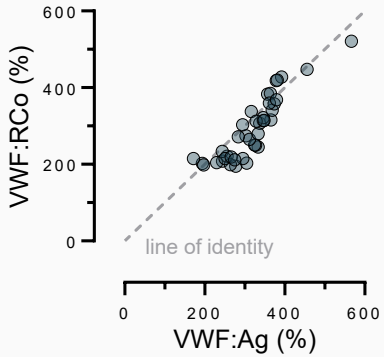
Observations across NHP studies[1] - FVIII Accumulates together with VWF

VWF accumulation vs gender

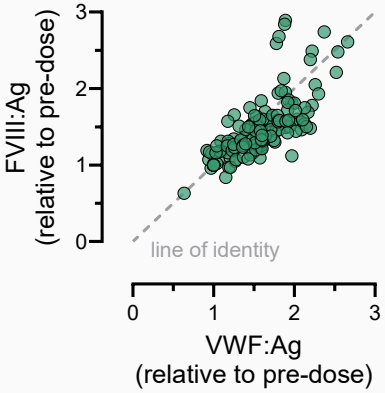


VWF:Ag at all timepoints ≥ day 8 (i.e., at full accumulation) across NHP studies

VWF:RCo follows VWF:Ag



FVIII follows VWF

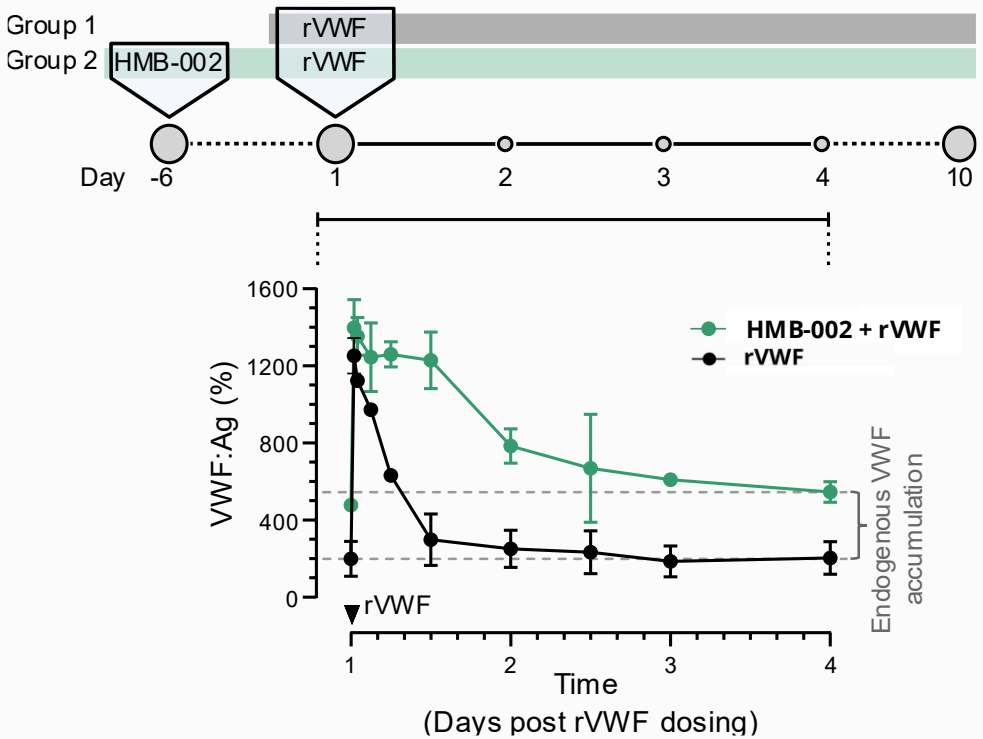


[1] available data from PK, DRF, and 4w tox studies

HMB-002 Extends the Half-life of Recombinant VWF in Non-Human Primates

Extended half-life of rVWF in the presence of HMB-002

Group 1 400 IU/kg rVWF (day 1)
Group 2 30 mg/kg (IV) HMB-002 (day -6) → 400 IU/kg rVWF (day 1)
(1 male + 1 female cynomolgus monkey/group)



Group	Half-life of rVWF (hrs)
rVWF alone	4.3
HMB-002 + rVWF	12.9

Key observations

Three-fold extension of rVWF (VWF:Ag) half-life in the presence of HMB-002

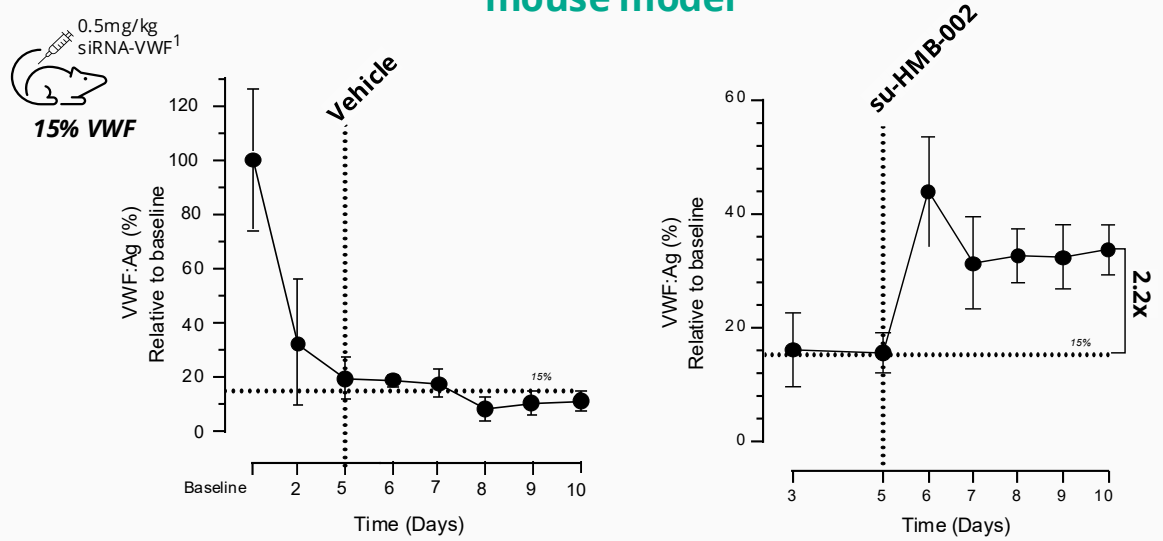
Two-fold elevation of endogenous VWF above baseline sustained throughout dosing and wash-out

Half-life extension matching the observed accumulation of endogenous VWF in this and other studies

VWF:Ag using ELISA and human plasma calibrator

HMB-002 Surrogate Antibody Induces VWF Accumulation in a type 1 VWD Mouse Model and Enhances Hemostatic Potential

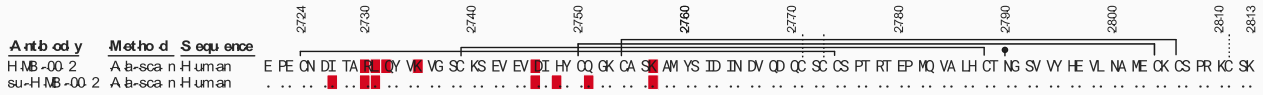
HMB-002 surrogate induces VWF accumulation in a Type 1 VWD mouse model



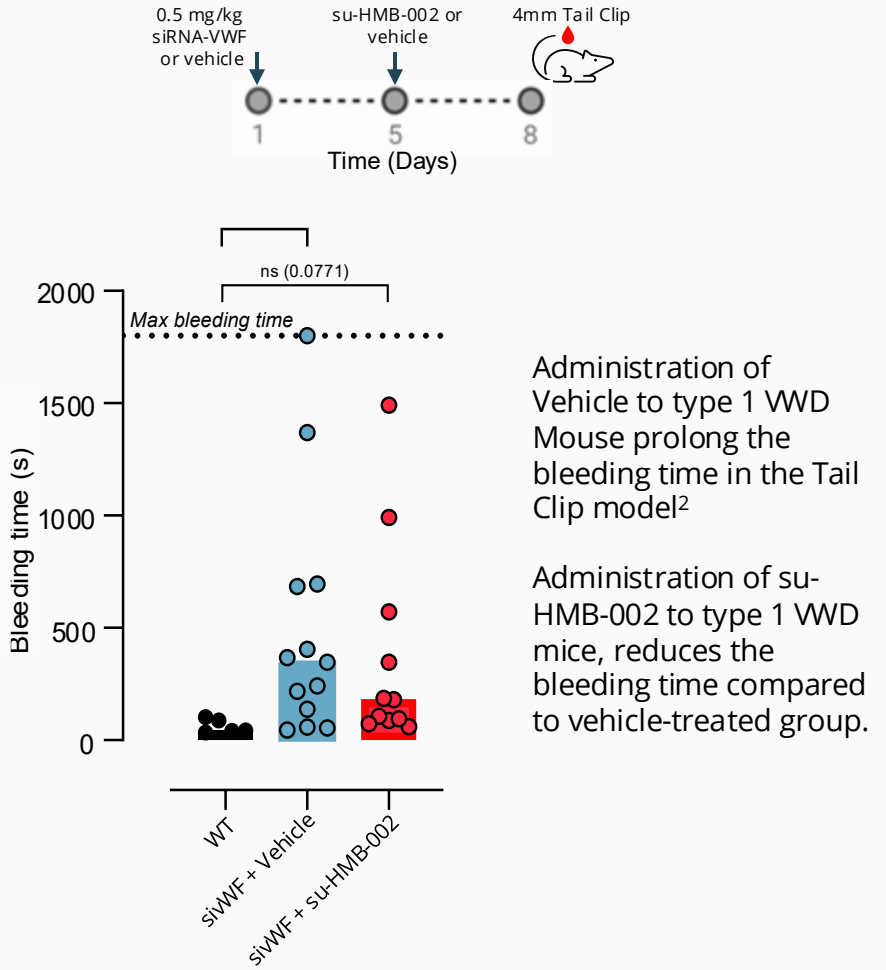
HMB-002 surrogate antibody (su-HMB-002)

HMB-002 does not bind to mouse VWF

The surrogate antibody (su-HMB-002) targets the VWF CK domain, with an epitope overlapping that of HMB-002, and binds with high affinity to mouse VWF



HMB-002 surrogate reduces the bleeding time in the Tail Clip model



Administration of Vehicle to type 1 VWD Mouse prolong the bleeding time in the Tail Clip model[2]

Administration of su-HMB-002 to type 1 VWD mice, reduces the bleeding time compared to vehicle-treated group.

References: 1. Jongejan YK, et al. Blood Adv. 2023; 2. Holmberg HL, et al. J Thromb Haemost. 2009.

VWF:Ag using ELISA and human plasma calibrator. VWFlow mouse model. C57BL/6 mice treated with 0.5 mg/kg sivWF

Conclusion & Acknowledgement

HMB-002

- Monovalent (one-arm) human antibody designed to bind and accumulate endogenous circulating VWF

In vitro and *in vivo* studies demonstrate

- Selective binding of HMB-002 to the C-terminal CK domain of VWF
- Key VWF functions retained when bound to HMB-002
- Accumulation of endogenous VWF and FVIII to about 2-fold of pre-dose level in cynomolgus monkey
- HMB-002 extends the half-life of recombinant VWF in cynomolgus monkey
- HMB-002 Surrogate Antibody Induces VWF Accumulation in a Type 1 VWD Mouse Model and Enhances Hemostatic Potential

Thank you to Hemab Therapeutics (Prafull S. Gandhi, Caroline Rasmussen, Rane A. Harrison, Emil Poulsen, Lars Holten-Andersen, Catherine J. Rea, Benny Sorensen, Henrik Ostergaard), **UMC Utrecht** (Minka Zivkovic, Rolf T. Urbanus), **Synapse Research Institute** (Dana Huskens, Mark Roest), and **SARomics Biostructures** (Anais Naretto)

Sponsor: Hemab Therapeutics

Additional Evidence @ ISTH

3 Poster Presentations
(PB1432, PB1460, PB1373)

2 Oral Presentations
(LB 01.4, OC 59.5)

NOW ENROLLING: US, UK, AUS

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)*

Learn more at Hemab.com

LATE BREAKER: 10:15AM tomorrow

Interim results from VELORA Pioneer Phase 1

Thank you