WFH COMPREHENSIVE CARE SUMMIT
New Developments in Bleeding Disorders and MSK
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Elevating Levels of Endogenous Circulating von Willebrand Factor (VWF)

The Potential of HMB-002 as Prophylactic Treatment of von Willebrand Disease (VWD)

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Disclosures for Benny Sorensen

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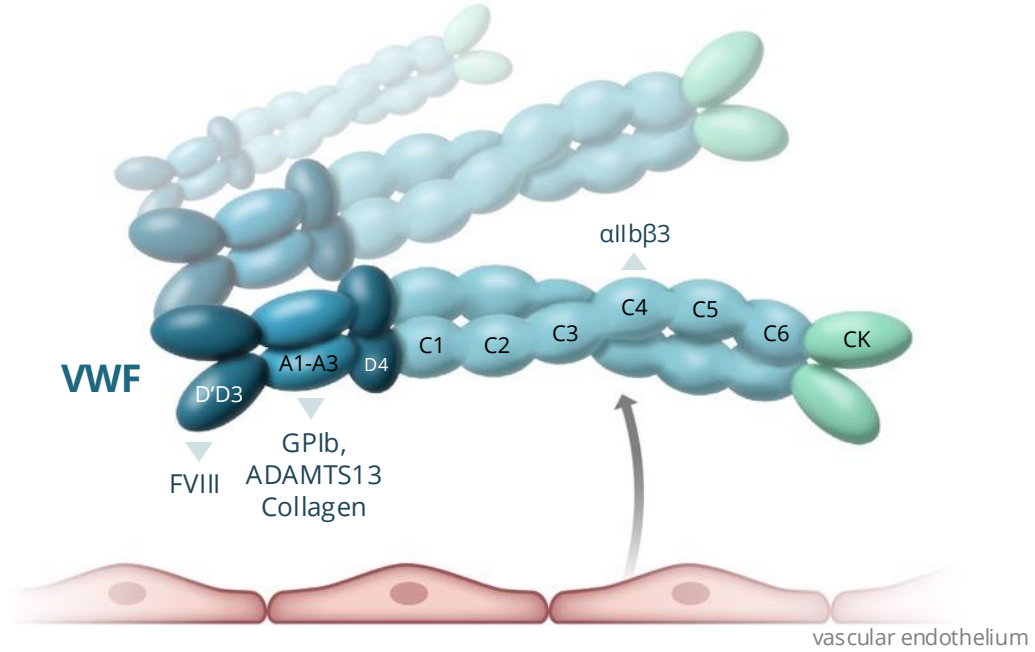
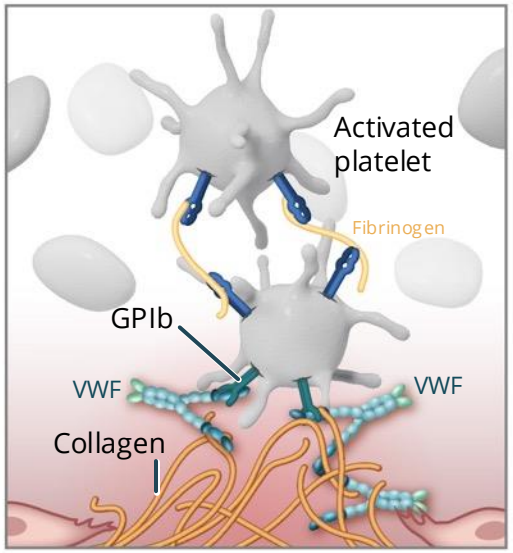
Research Support	No relevant conflicts of interest to declare
Director, Officer, Employee	Hemab Therapeutics
Shareholder	Hemab Therapeutics
Honoraria	No relevant conflicts of interest to declare
Advisory Committee	No relevant conflicts of interest to declare
Consultant	No relevant conflicts of interest to declare

#wfhCCS

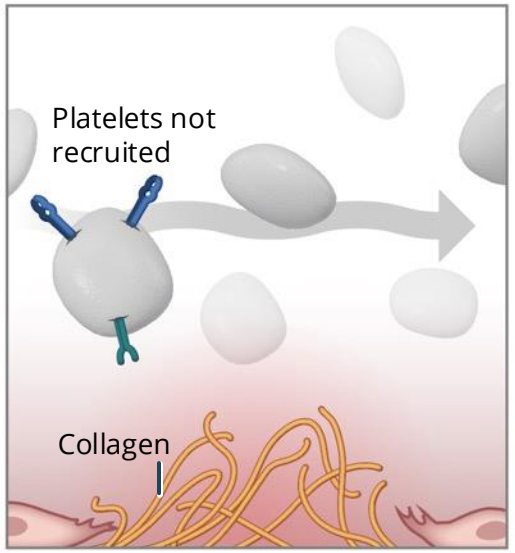
Von Willebrand Disease – A Bleeding Disorder with Unmet Needs



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

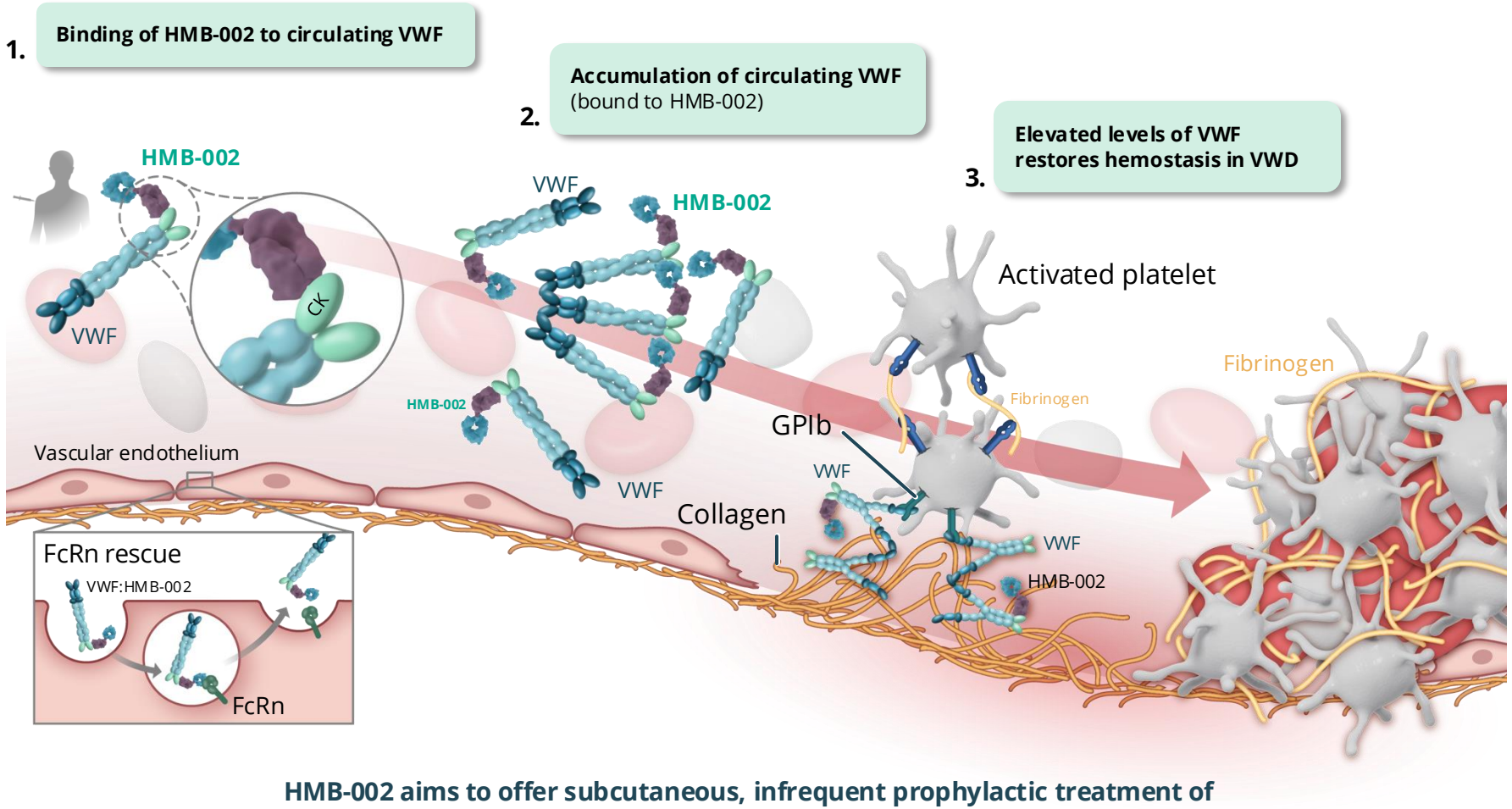
Functions of HMB-002

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

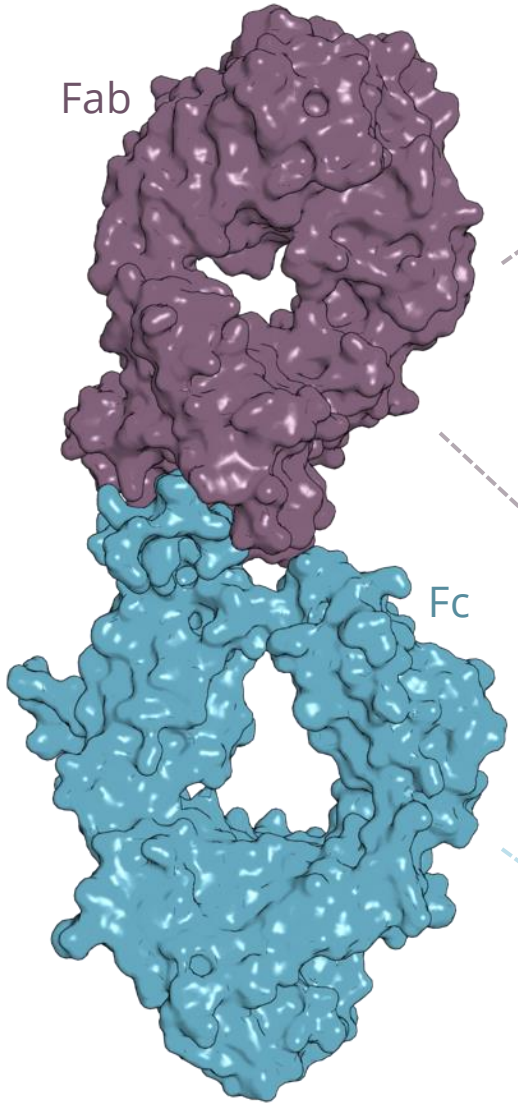
- *Primary Hemostasis*
  Elevated VWF levels enhance platelet recruitment to site of injury
- *Secondary Hemostasis*
  Accumulated FVIII further supports clot formation by contributing to secondary hemostasis



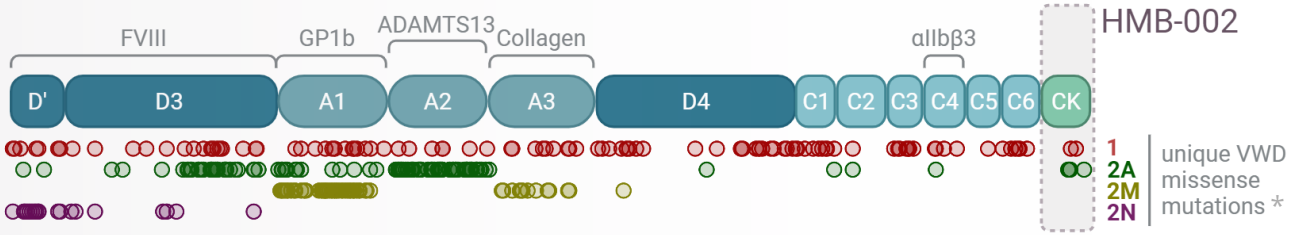
HMB-002 aims to offer subcutaneous, infrequent prophylactic treatment of people with VWD

Other studies applying a target accumulation strategy: Gandhi (2024) Nat Cardiovasc Res. 3(2):166–185 / McCluskey (2024) Haematologica. doi: 10.3324/haematol.2024.286076

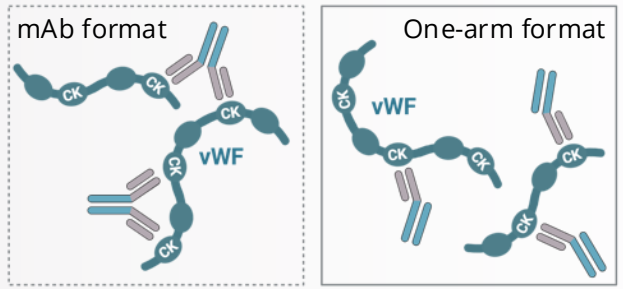
HMB-002 Designed to Bind the C-terminal CK Domain of VWF

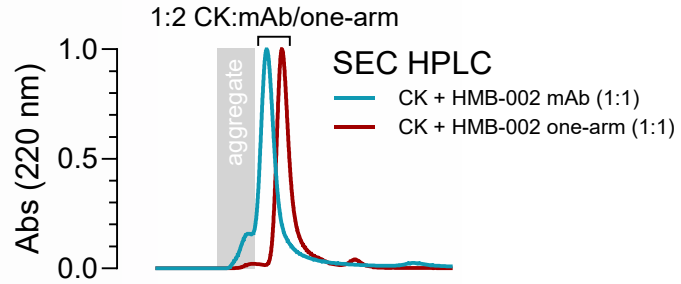


Targeting the C-terminal CK domain in VWF



Monovalent (one-arm) human antibody format





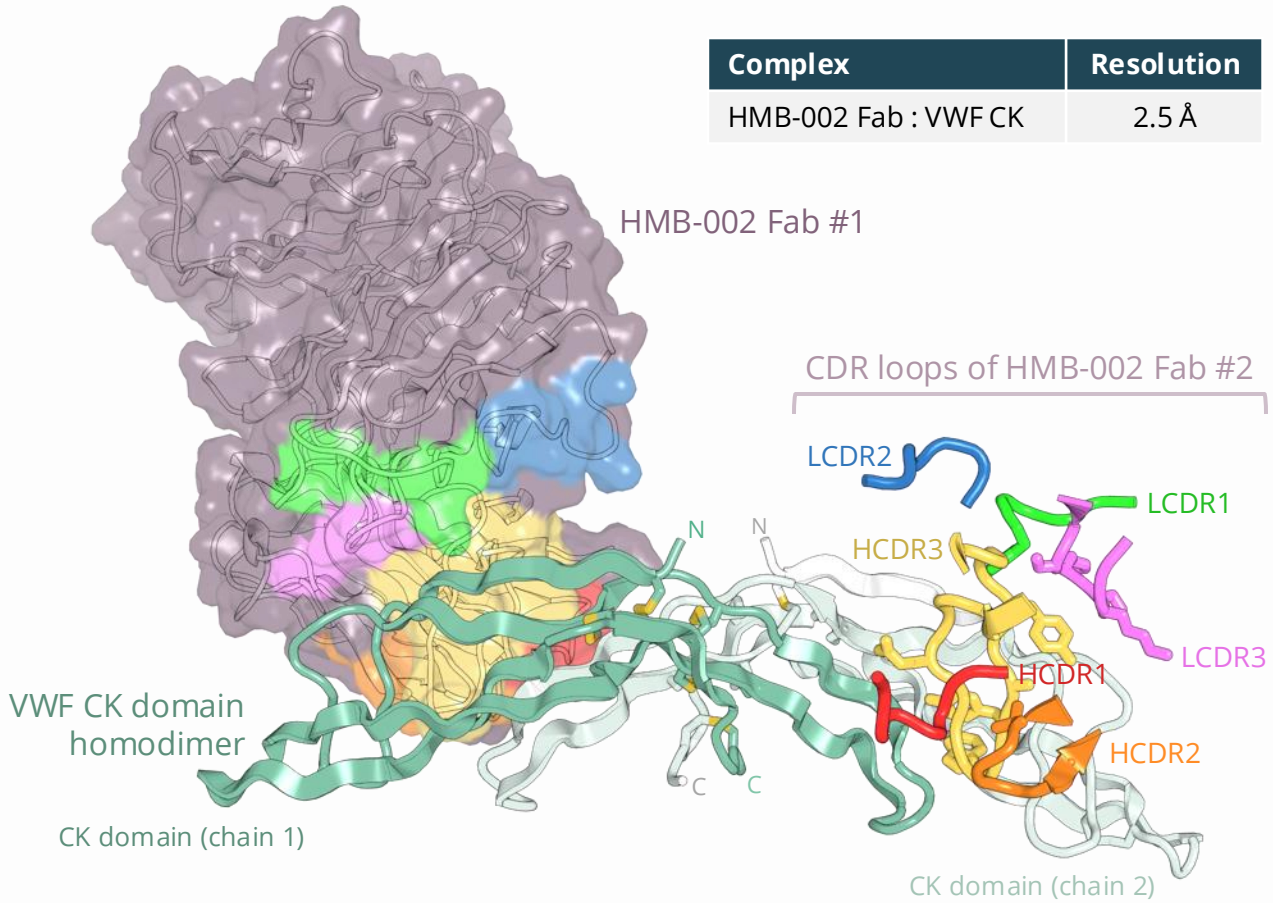
Human IgG4 + Fc effector silencing

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

*de Jong (2017) Thrombosis Research, 159:65; **abstract submitted to ISTH 2025 (Washington DC).

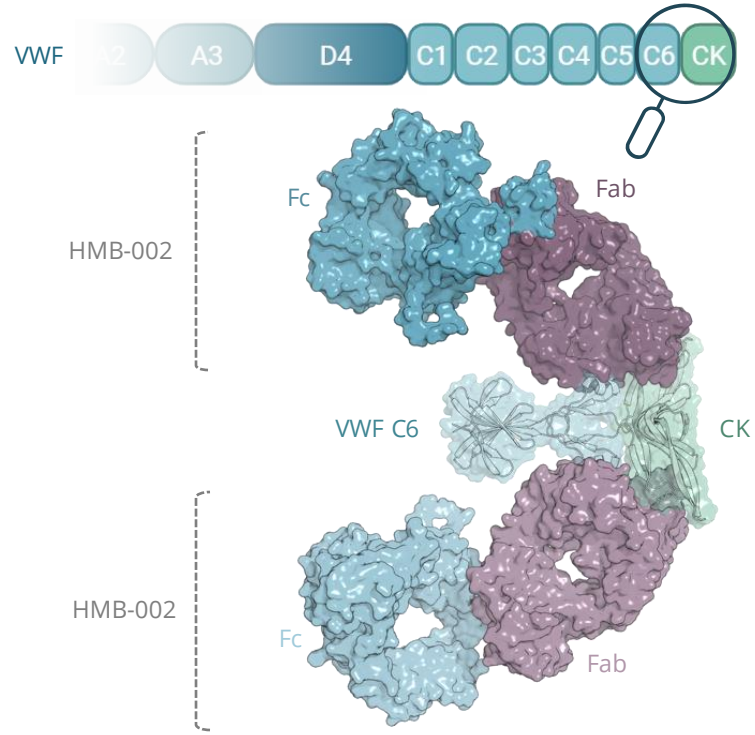
HMB-002 Selectively Binds to Epitope in the VWF CK Domain

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*

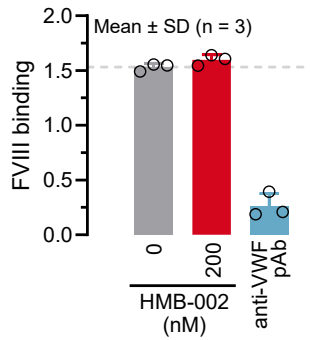


K_D for HMB-002 binding at pH 7.4 and 25°C (SPR)	VWF CK	Plasma-derived VWF
	0.6 nM	0.1 nM

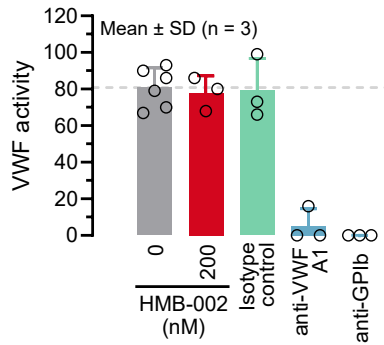
*Chen (2022) J Struct Biol, 214:107923 / Zhou (2014) Blood, 123:1785 / Scapin (2015) Nat Struct Mol Biol, 22:953

VWF Retains Key Functions in Presence of HMB-002

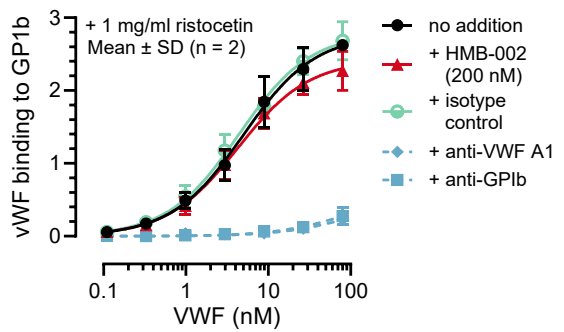
1 FVIII:VWF binding



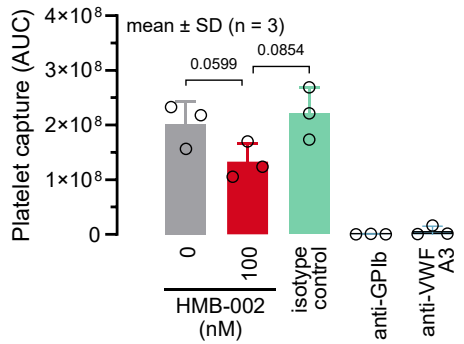
2 VWF:RCo activity

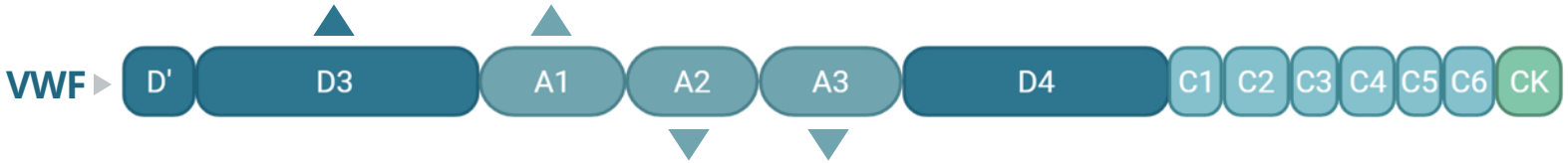


VWF:GP1b binding (ELISA)

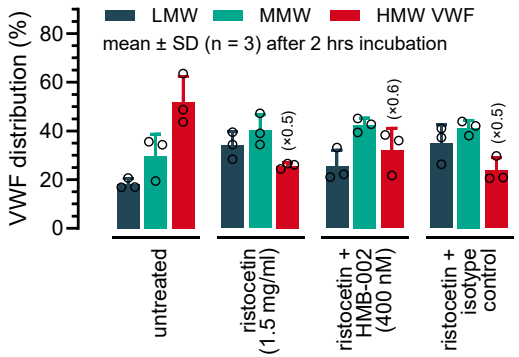


5 Whole-blood platelet capture on collagen surface at high shear

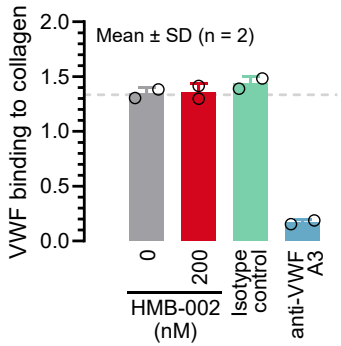




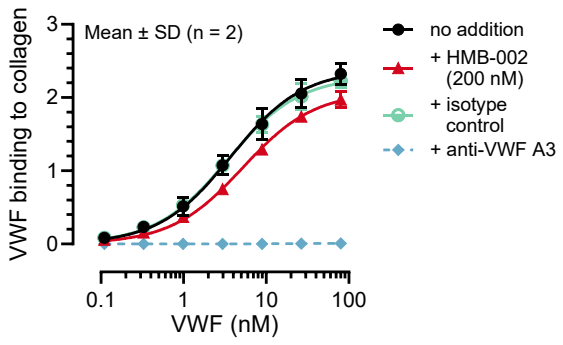
3 ADAMTS13 processing (plasma)



4 VWF:CBA



VWF:Collagen III binding (ELISA)

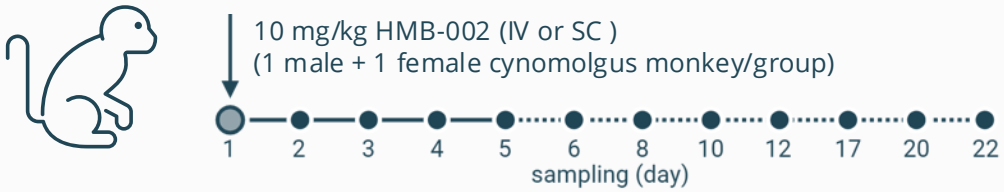


Methods

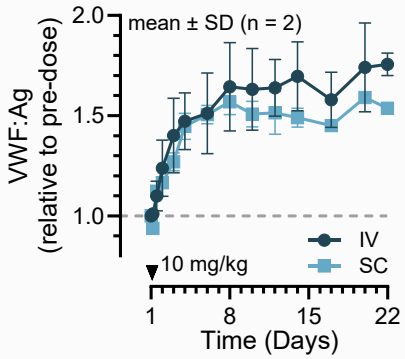
FVIII:VWF binding	Asserachrom® VWF:FVIIIB
VWF:RCo activity	STA®-VWF:RCo assay in citrated human plasma
VWF:GPIb binding	ELISA with immuno-captured GPIb ectodomain and ristocetin
ADAMTS13 processing	Citrated human plasma with ristocetin (2-h incubation)
VWF:CBA	ZYMUTEST™ VWF:CBA (collagen I/III)
VWF:Collagen 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

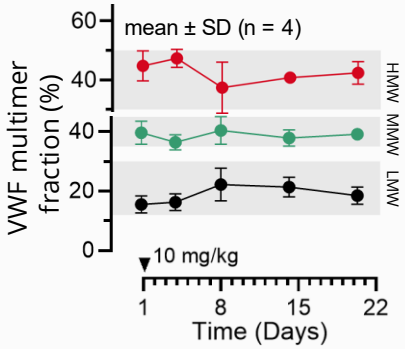
Prolonged VWF accumulation with retained multimer pattern after single-dose of HMB-002



VWF accumulation



VWF multimer distribution

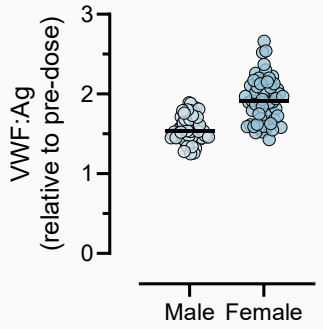


Assays

- 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)

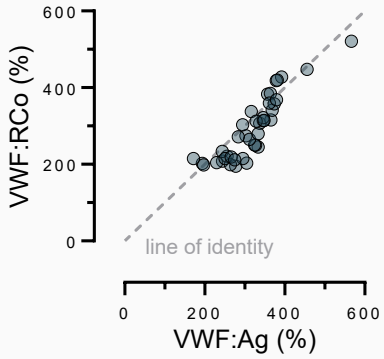
Observations across NHP studies[1] - FVIII Accumulates together with VWF

VWF accumulation vs gender

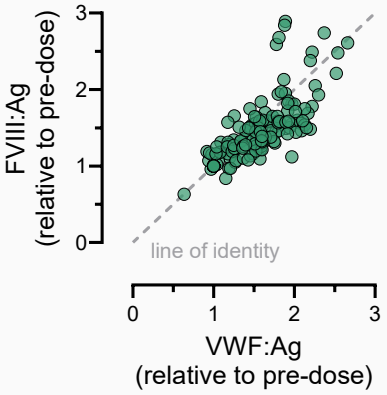


VWF:Ag at all timepoints ≥ day 8 (i.e., at full accumulation) across NHP studies

VWF:RCo follows VWF:Ag



FVIII follows VWF



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

VWD 360: Leading the Way with Largest VWD Study to Date

VWD 360
The Lived Experience of People with von Willebrand Disease

VWD 360
The Lived Experience of People with von Willebrand Disease

611
respondents

15
countries

Study Design

Three-part study:

(1) Online survey (n=611)

(2) In-depth interviews (n=30)
focus on severe Type 1 & 2

(3) 30-day bleed diary (n=53)

Study Objectives

- Assess the natural history and burden of VWD, including:
  - bleeding frequency
  - quality of life
  - access to care
- Identify unmet needs across VWD subtypes

Conclusions & Acknowledgements

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

Next step

✓First human dosed in Feb-2024

❑ Enroll ongoing clinical trials in UK, US, and Australia

Now Enrolling: VWD Type 1

United Kingdom	United States	Australia
Richmond Pharmacology	Arkansas Children's Hospital	Fiona Stanley Hospital, Perth
	Emory University Hospital	Royal Prince Alfred, Sydney
	Innovative Hematology, Indiana	The Alfred Hospital, Melbourne
	Mayo Clinic – Rochester	
	Oregon Health & Science University	
	Phoenix Children's Hospital	
	Tulane University School of Medicine	
	University of Miami	
	University of Michigan	
	University of Texas Southwestern Medical Center	
	Washington Center for Bleeding Disorders	