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Favorable nonclinical safety profile of HMB-002 for prophylactic treatment of Von Willebrand disease

Caroline Rasmussen[1], Henrik Østergaard[1], Lars Holten-Andersen[1], Tine Holst Kjeldsen[1], Pruthvi Nagilla[1], Jacob Fredsted[1], Emil Poulsen[1], Catherine Rea[1], Jennifer Sims[2], Mattias Häger[1]

[1]Hemab Therapeutics, Copenhagen, Denmark, [2]iBiologix, Basel, Switzerland

Contact details
Caroline Rasmussen
caroline@hemab.com

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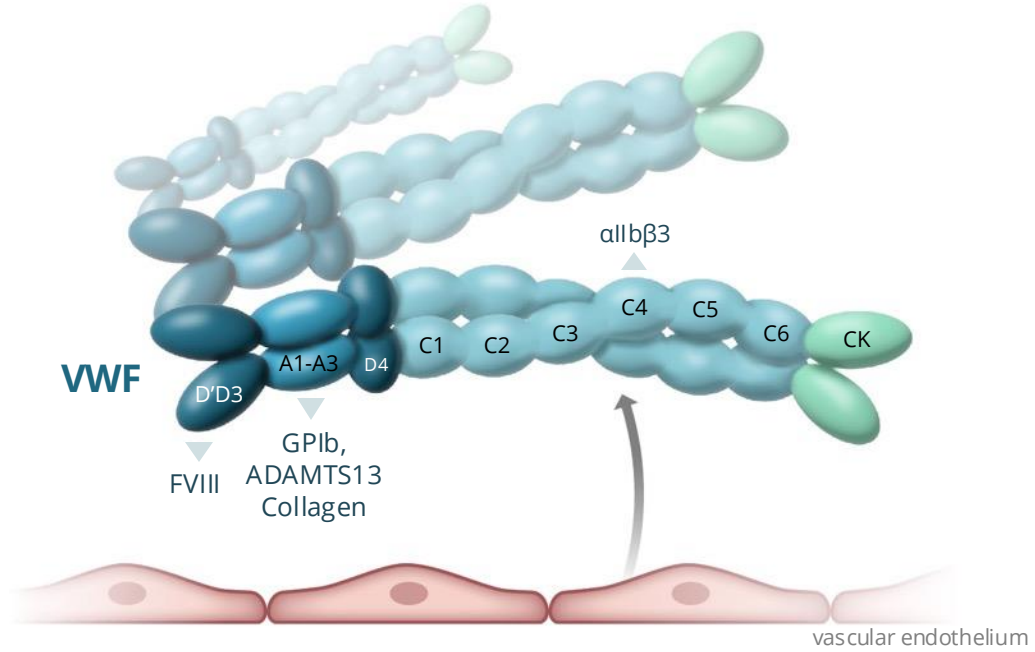
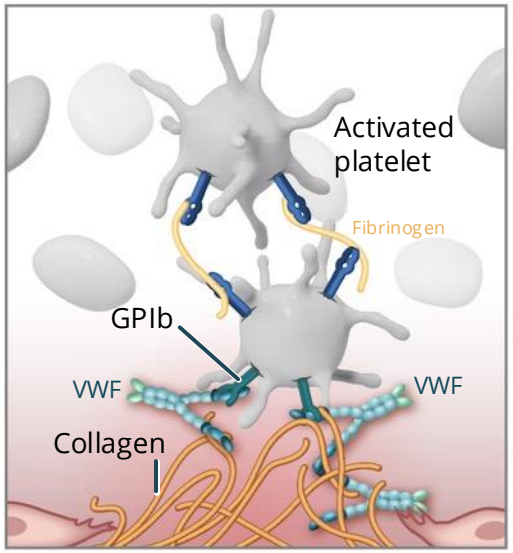
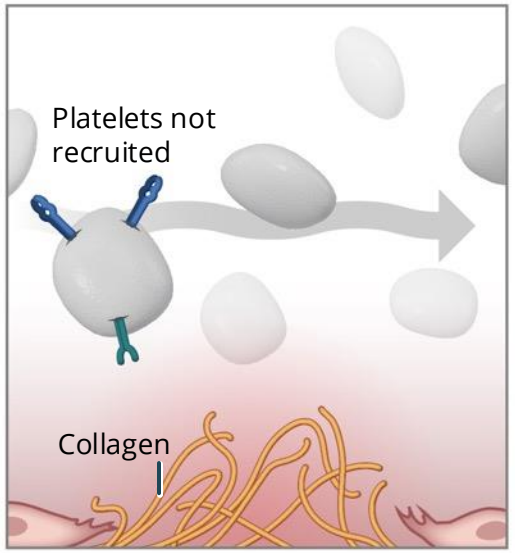
Von Willebrand Disease – A Bleeding Disorder with Unmet Needs



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

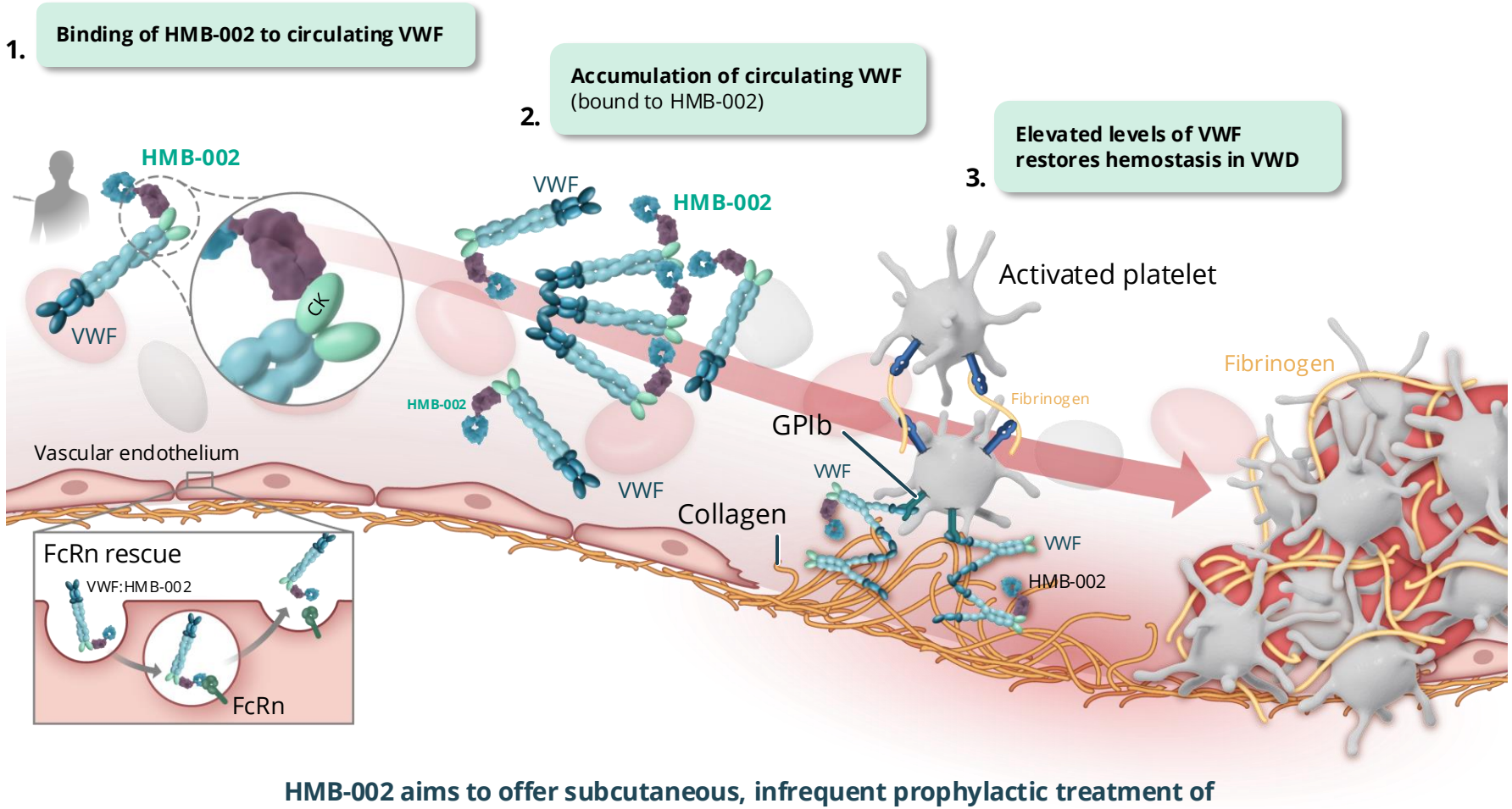
Functions of HMB-002

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

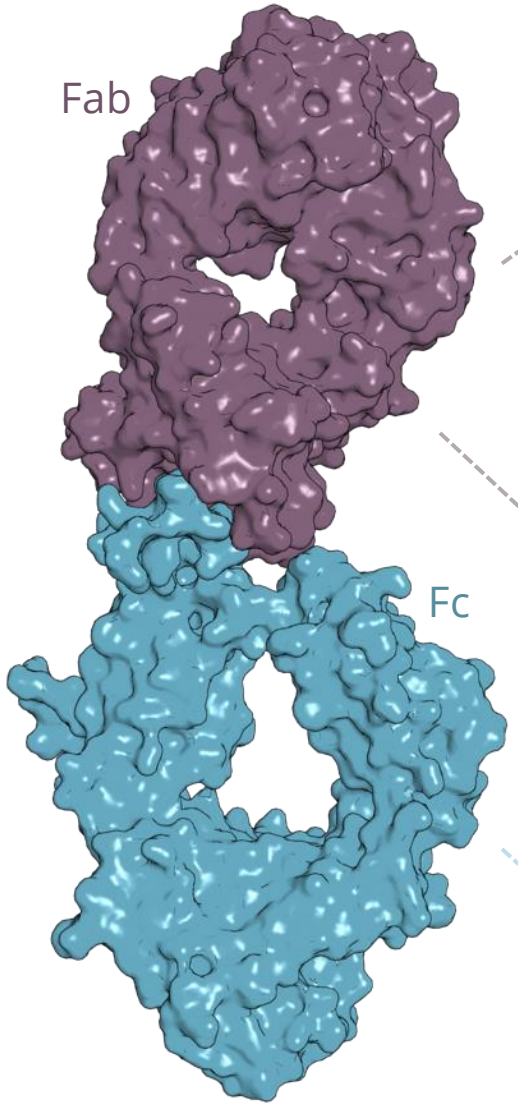
- *Primary Hemostasis*
  Elevated VWF levels enhance platelet recruitment to site of injury
- *Secondary Hemostasis*
  Accumulated FVIII further supports clot formation by contributing to secondary hemostasis



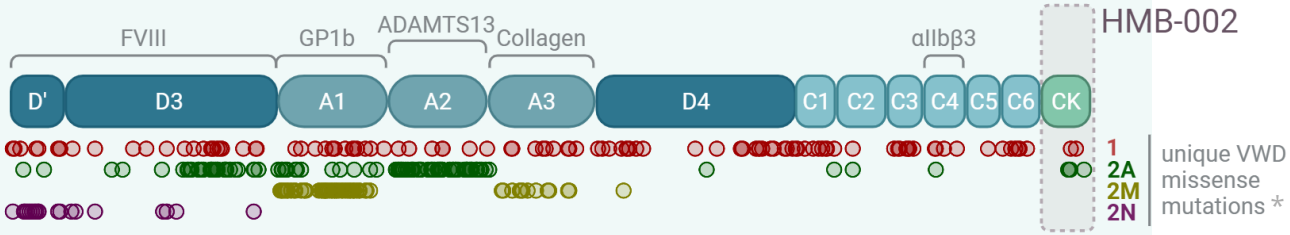
HMB-002 aims to offer subcutaneous, infrequent prophylactic treatment of people with VWD

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.
CK =cysteine knot; FcRn = neonatal fragment crystallizable receptor; FVIII = coagulation factor VIII; VWF = Von Willebrand Factor; VWD = Von Willebrand Disease.

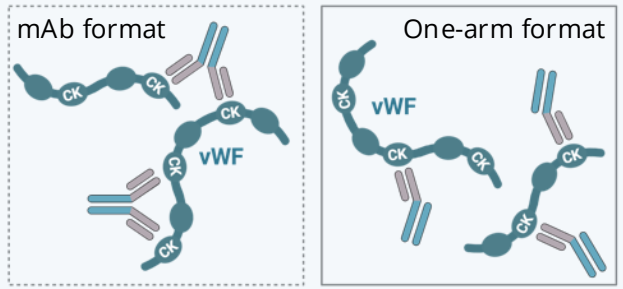
HMB-002 – A Monovalent Human IgG4 with Fc effector Silencing Designed to Bind the C-terminal CK Domain of VWF



Targeting the C-terminal CK domain in VWF



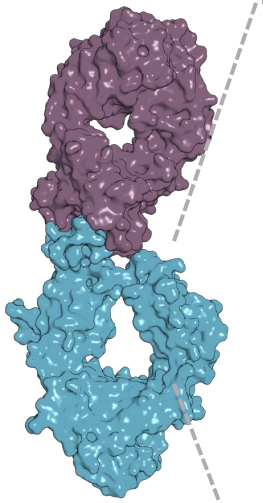
Monovalent (one-arm) human antibody format



Human IgG4 + Fc effector silencing

* de Jong A, et al. Thromb Res. 2017;159:65.
CK =cysteine knot; Fab = fragment antigen-binding; Fc = fragment crystallizable; FVIII = coagulation factor VIII; VWF = Von Willebrand Factor; IgG4 = immunoglobulin G4; mAb = monoclonal antibody.

Comprehensive Nonclinical Safety Evaluation of HMB-002 Demonstrates No Adverse Findings, No Immunotoxicity, and No Off-target Binding



HMB-002

	Nonclinical Safety Evaluation	*Key Findings*

In Vivo	• **Repeat-Dose Toxicity** studies in monkeys
	  ○ Up to 13 weeks of duration
	  ○ Safety and PK/PD assessment
		No adverse findings at any dose levels
		(exposure ratio 9.7-fold the simulated clinical exposure after administration of 300 mg)

In Vitro & Ex Vivo	• **Off-target binding** (6,505 human proteins) • **Fc-γ and FcRn receptor binding** (human receptors) • **Tissue cross reactivity** (panel of human tissues) • **Complement & platelet activation** (human whole blood) • **Cytokine release** (human whole blood)	**No off-target binding** **No immunotoxicity**

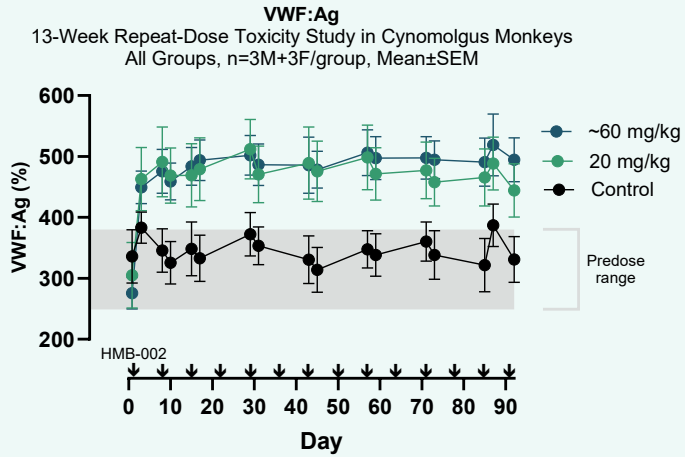
Fc = fragment crystallizable; FcRn = neonatal fc receptor; PD = pharmacodynamic; PK = pharmacokinetic.

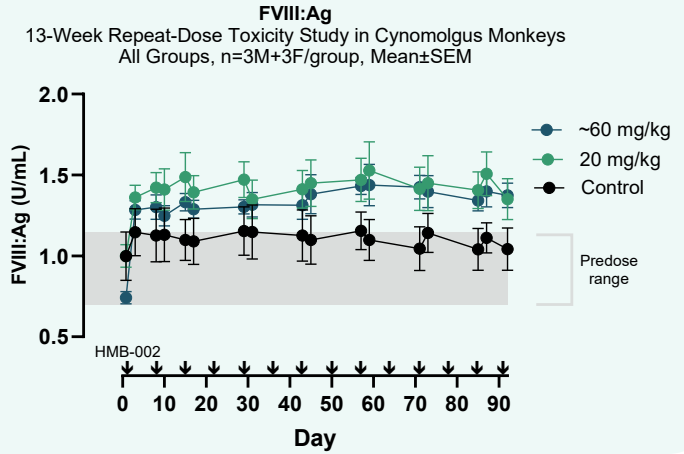
VWF Accumulation without Functional Compromise in Cynomolgus Monkey

Targeting C-terminal CK domain | **Monovalent human antibody format** | Human IgG4 + Fc effector silencing

- In vitro studies demonstrate no interference with key physiological activities of VWF*
- Sustained stable accumulation of endogenous VWF and FVIII to about 2-fold of predose level for the duration of the 13-week toxicity study
- Parallel increase in VWF antigen and activity and FVIII
- Majority of cynomolgus monkeys developed ADA without impact on PK or PD

Maintained VWF activity consistent with targeting the CK-domain with a monovalent antibody





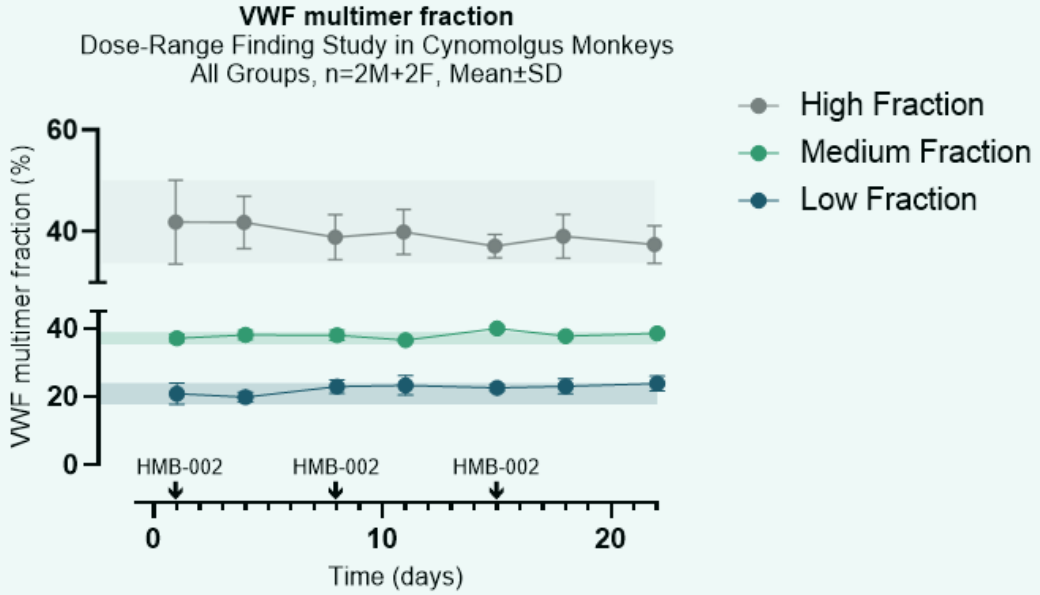
*Oral presentation OC 08.4: Elevating Levels of Endogenous Circulating von Willebrand Factor (VWF): The Potential of HMB-002 as a Prophylactic Treatment of Von Willebrand Disease (VWD)
ADA = anti-drug antibody; CK =cysteine knot; Fc = fragment crystallizable; FVIII = coagulation factor VIII; FVIII:Ag; FVIII antigen by ELISA and human plasma calibrator; IgG4 = immunoglobulin G4; PD = pharmacodynamic; PK = pharmacokinetic; VWF = Von Willebrand Factor; VWF:Ag = VWF antigen by ELISA and human plasma calibrator.

No Off-Target Effect, No Tissue Cross Reactivity and No Impact on VWF Multimer Distribution Across In Vivo, In Vitro and Ex Vivo Toxicity Studies

Targeting C-terminal CK domain | **Monovalent human antibody format** | Human IgG4 + Fc effector silencing

- Distribution of VWF multimers remain similar to predose distribution after administration of HMB-002 in cynomolgus monkeys
- No off-target effects in monkeys or in in vitro evaluation of 6,505 human proteins
- No tissue cross-reactivity in human tissues

High selectivity and preserved VWF multimer distribution consistent with targeting the CK-domain with a monovalent antibody



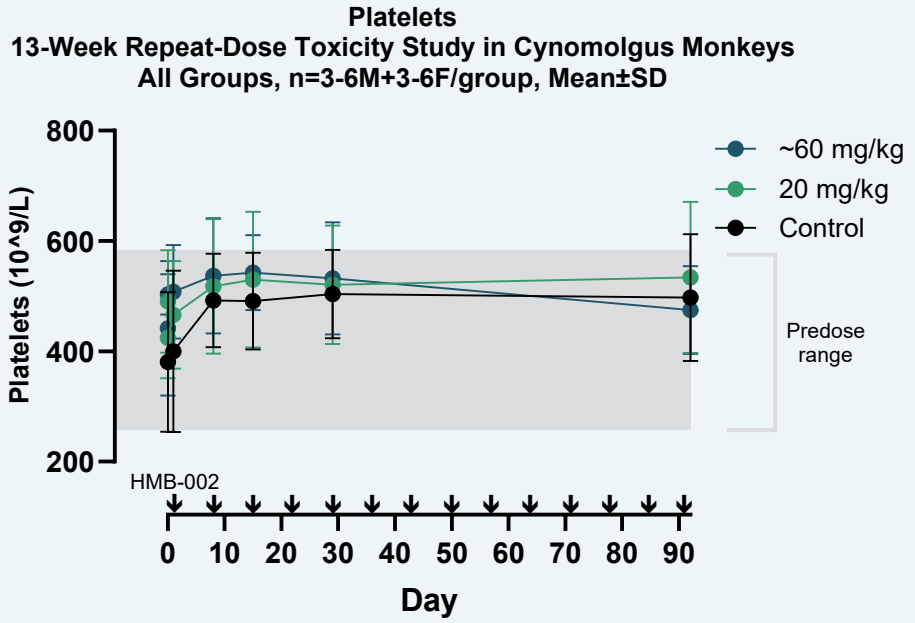
CK =cysteine knot; Fc = fragment crystallizable; IgG4 = immunoglobulin G4; VWF = Von Willebrand Factor; VWF multimer by gel electrophoresis and immunostaining.

No Changes in Coagulation, Hematology and Histopathology in Toxicity Studies in Cynomolgus Monkeys

Targeting C-terminal CK domain | **Monovalent human antibody format** | **Human IgG4 + Fc effector silencing**

- No changes in APTT, PT, fibrinogen and D-Dimer related to HMB-002
- No change in hematology incl. platelets related to HMB-002
- No histopathological evidence of thrombi and immune complex deposition

No apparent Fc-y receptor-related findings consistent with a monovalent human IgG4 Fc effector silenced antibody



APTT = activated partial thromboplastin time; CK =cysteine knot; F = female; Fc = fragment crystallizable; IgG4 = immunoglobulin G4; M = male; Platelets by flow cytometry; PT = prothrombin time; VWF = Von Willebrand Factor.

No Immunotoxicity in In Vitro, Ex Vivo and In vivo Toxicity Studies

Targeting C-terminal CK domain | Monovalent human antibody format | **Human IgG4 + Fc effector silencing**

- No effect on complement activation, platelet activation, or cytokine release in cynomolgus monkeys and in human whole blood
- No or highly-reduced binding to panel of human Fc-γ receptors in comparison to control IgG4 antibody
- Retained pH-dependent binding to FcRn

No apparent Fc-γ receptor-related findings consistent with a human IgG4 Fc effector silenced antibody

K_D (M)	HMB-002	Approved standard IgG4 antibody
hFcγRIIIA$_{176F}$	NB	1.10 E-05
hFcγRIIIA$_{176V}$	*	5.18 E-06
hFcγRIIIB	NB	*
hFcγRIIA$_{167R}$	NB	9.35 E-06
hFcγRIIA$_{167H}$	*	1.11 E-05
hFcγRIIB	*	1.04 E-05
hFcγRI	NB	4.60 E-09
FcRn	pH 6: 1.10 E-06 pH 7.4: NB	pH 6: 1.38 E-06 pH 7.4: NB

* a low level of binding was observed but too weak to determine a K_D.
K_D = dissociation constant; NB = no binding.

CK =cysteine knot; Fc = fragment crystallizable; FcRn = neonatal fc receptor; IgG4 = immunoglobulin G4.

Conclusion & Acknowledgement

HMB-002

Monovalent (one-arm) human antibody designed to bind and accumulate endogenous circulating VWF, while preservation functionality and regulation

Favorable *nonclinical safety profile* – study results consistent with intended design of HMB-002

- High selectivity towards the CK domain
- Maintained VWF activity
- Preserved VWF multimer distribution
- No apparent Fc-γ receptor-related effects
- No adverse findings at any dose levels (exposure ratio 9.7-fold the simulated clinical exposure after administration of 300 mg)

Thank you to Hemab Therapeutics (Henrik Østergaard, Lars Holten-Andersen, Tine Holst Kjeldsen, Pruthvi Nagilla, Jacob Fredsted, Emil Poulsen, Catherine Rea, Mattias Häger) and **iBiologix** (Jennifer Sims)

Sponsor: Hemab Therapeutics

Additional Evidence @ ISTH

3 Poster Presentations
(PB1432, PB1460, PB1373)

2 Oral Presentations
(LB 01.4, OC 08.4)

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

CK =cysteine knot; Fc = fragment crystallizable; VWF = Von Willebrand Factor; VWD = Von Willebrand Disease.