HMB-001

A novel bispecific antibody with potential for subcutaneous prophylactic treatment of multiple bleeding disorders - initial focus on Glanzmann Thrombasthenia (GT)

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Disclosure for Prafull S. Gandhi

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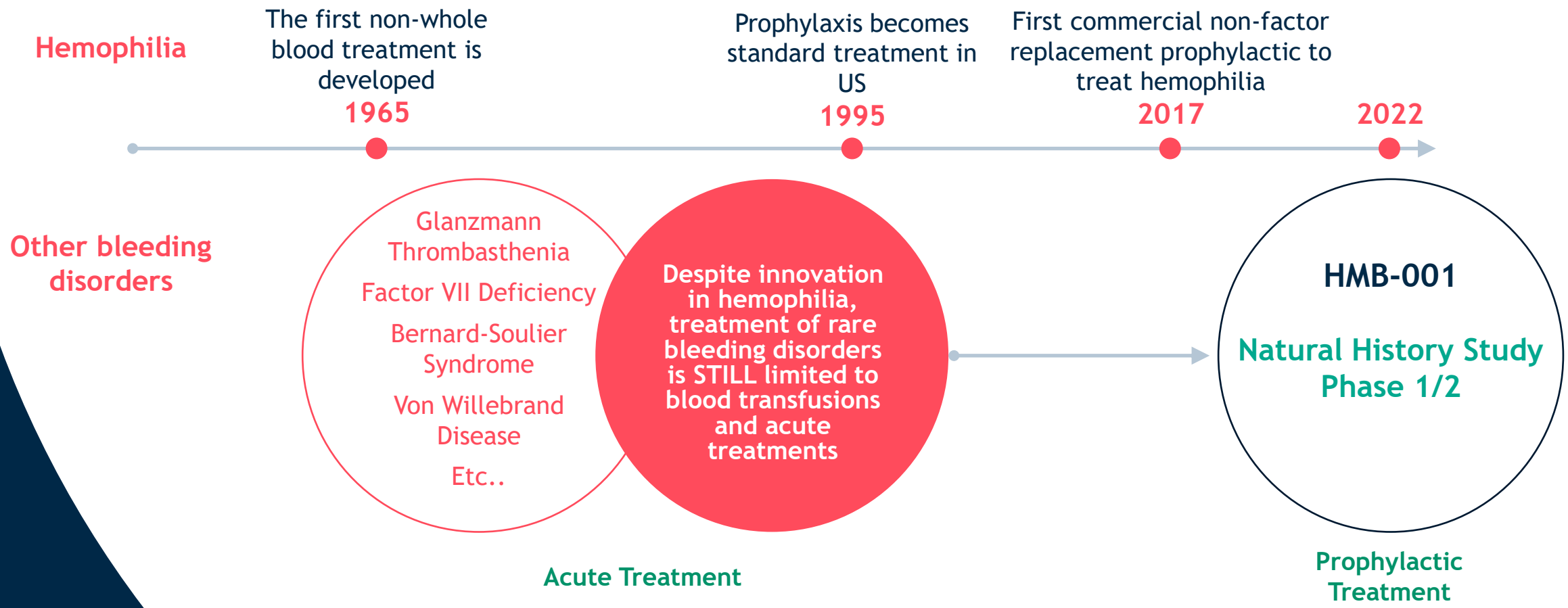
Shareholder	No relevant conflicts of interest to declare
Grant / Research Support	No relevant conflicts of interest to declare
Consultant	No relevant conflicts of interest to declare
Employee	Hemab Therapeutics
Paid Instructor	No relevant conflicts of interest to declare
Speaker bureau	No relevant conflicts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

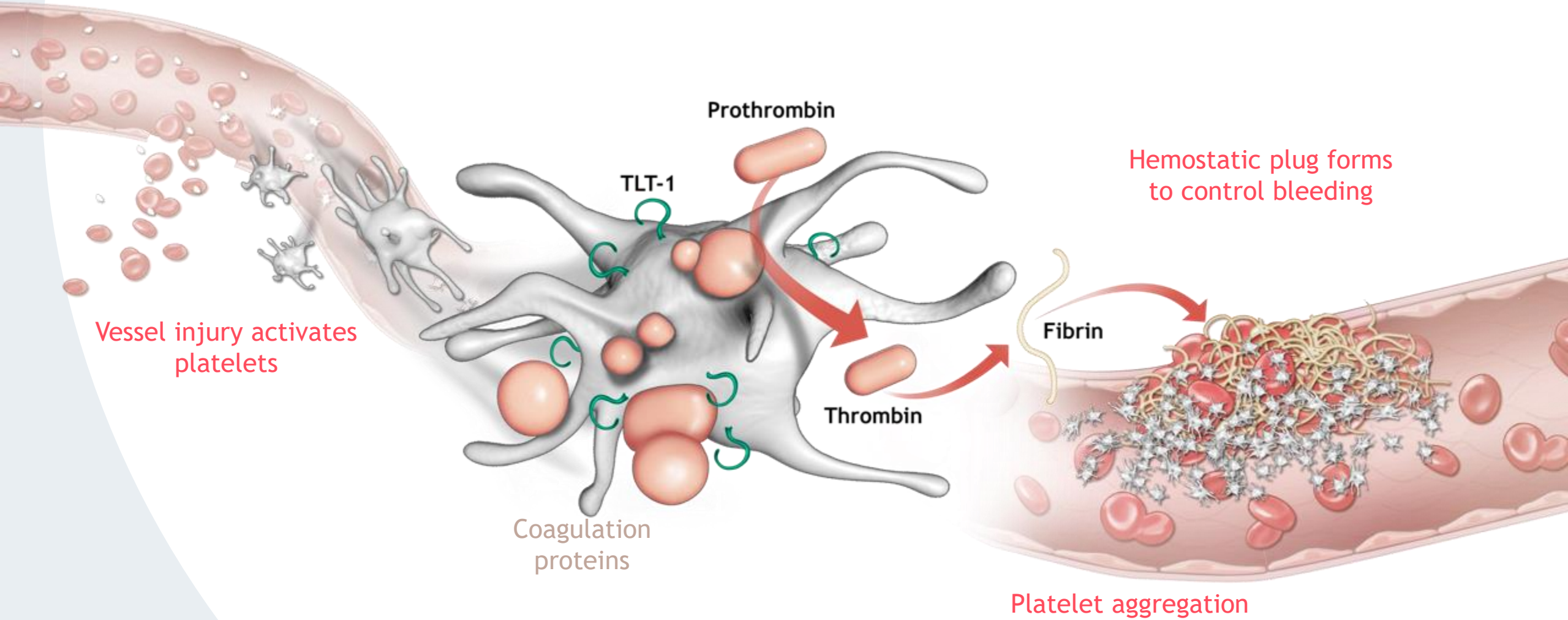
Presentation includes discussion of the following off-label use of a drug or medical device:
<N/A>

Prophylaxis is Not Available for People with Rare Bleeding Disorders



Healthy Hemostatic System

Controlling bleeding, preventing thrombosis



Vessel injury activates platelets

Coagulation proteins

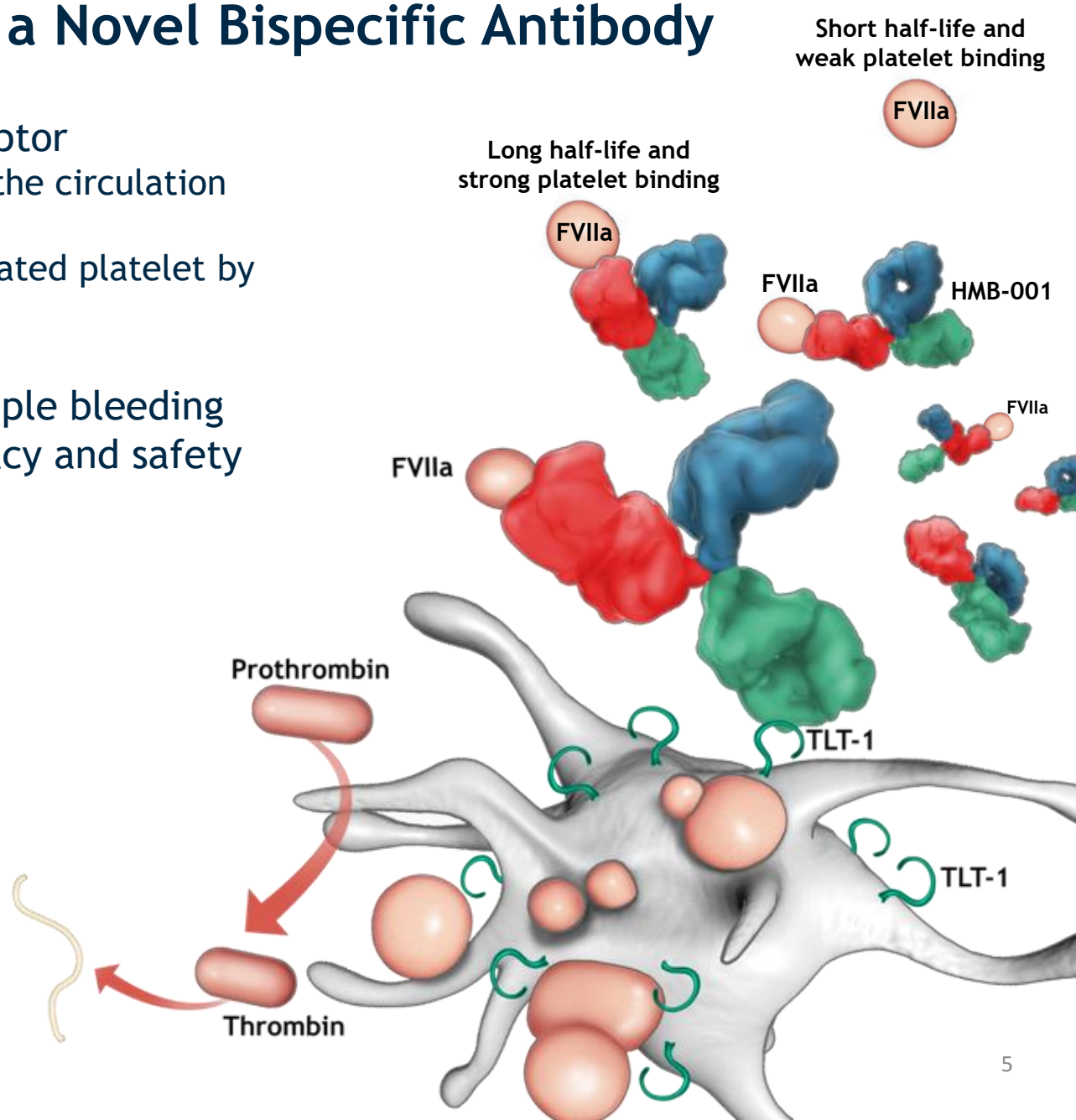
Hemostatic plug forms to control bleeding

Platelet aggregation

HMB-001 | Mechanism of Action of a Novel Bispecific Antibody

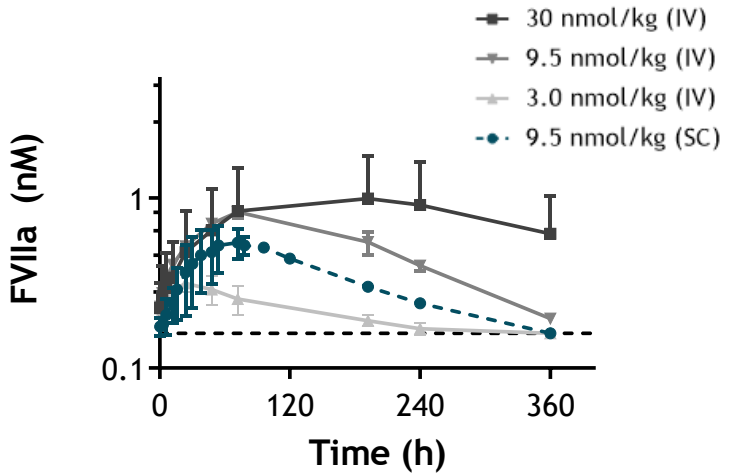
- HMB-001 binds endogenous FVIIa and TLT-1 receptor
  - Accumulate fully functional endogenous FVIIa in the circulation by the anti-FVIIa arm
  - Recruit endogenous FVIIa selectively on the activated platelet by the anti-TLT-1 arm

- HMB-001 is designed for prophylaxis across multiple bleeding disorders based on the clinically validated efficacy and safety of recombinant FVIIa



HMB-001 | Accumulates Endogenous FVIIa and Increase Potency via TLT-1 Platelet Targeting

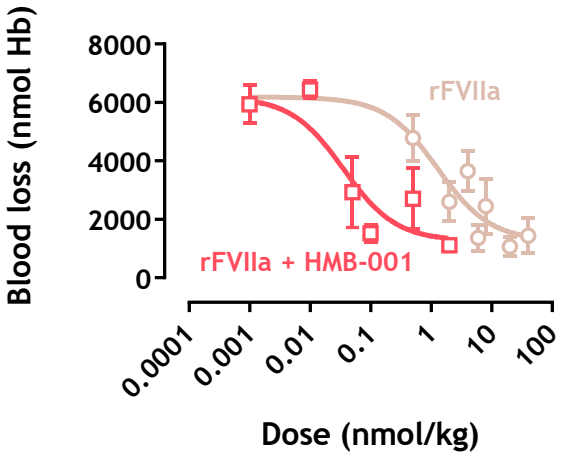
PK study in Cynomolgus Monkey
HMB-001 leads to accumulation of endogenous FVIIa



Study design:
- Study conducted in healthy NHP (cynomolgus monkey)
- Single bolus injection IV and/or SC, n=2

Conclusions:
- A dose-dependent accumulation of endogenous FVIIa is observed
- No adverse event were observed. No safety signal have been detected including changes in platelet counts, fibrinogen levels, or d-dimers

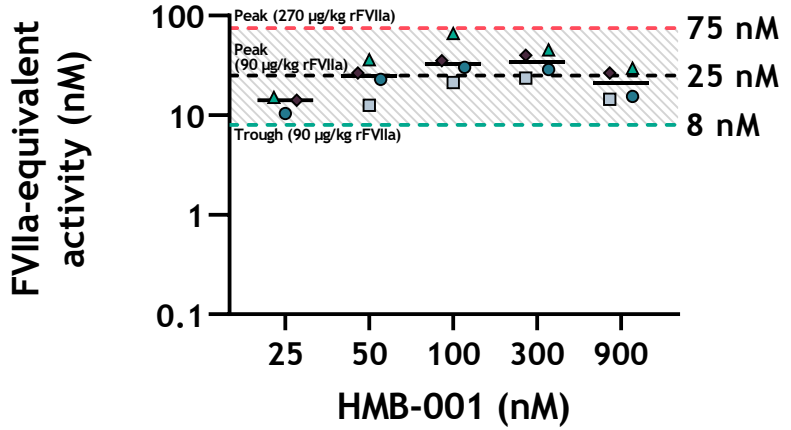
In vivo effect in Mouse tail bleeding model
HMB-001 potentiates effect of rFVIIa



Study design:
- Study conducted in haemophilia A mice (F8KO) with TLT-1 KOKI
- Compounds, rFVIIa or rFVIIa:HMB-001 (1:1), administered 5 min prior to injury
- Using Tail Vein Transection (TVT) bleeding model, blood loss from lateral vein and bleeding time were measured

Conclusion:
- HMB-001 leads to substantial potentiation of the effect of rFVIIa in mice

HMB-001 raises activity of FVIIa to therapeutic levels in whole blood ex *vivo* assay

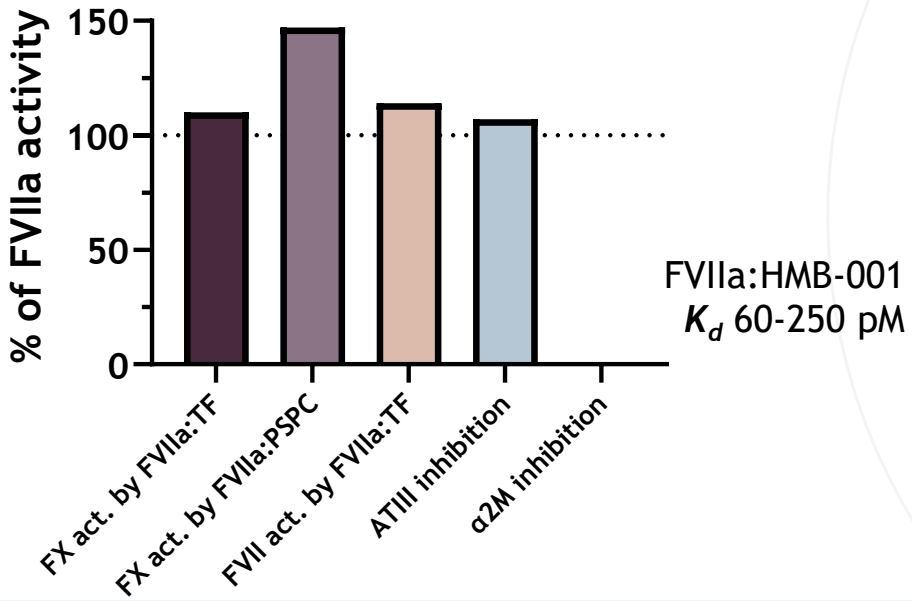


Study design:
- FVIIa-equivalent activity at relevant steady-state levels of FVIIa and HMB-001, predicted by NHP PK, was measured by Thromboelastography (R-time) in HA-like blood from 4 donors

Conclusions:
- HMB-001 can provide significantly ≥8 nM FVIIa-equivalent activity and matches the FVIIa-equivalent activity observed immediately after a clinical IV dose of 90 – 270 µg/kg rFVIIa (25 – 75 nM FVIIa)
- No signs of hypercoagulability was observed at wide range of HMB-001 concentrations

HMB-001 | Anti-FVIIa Binding Site on FVIIa is Remote from Natural Substrate, Cofactor and Inhibitors

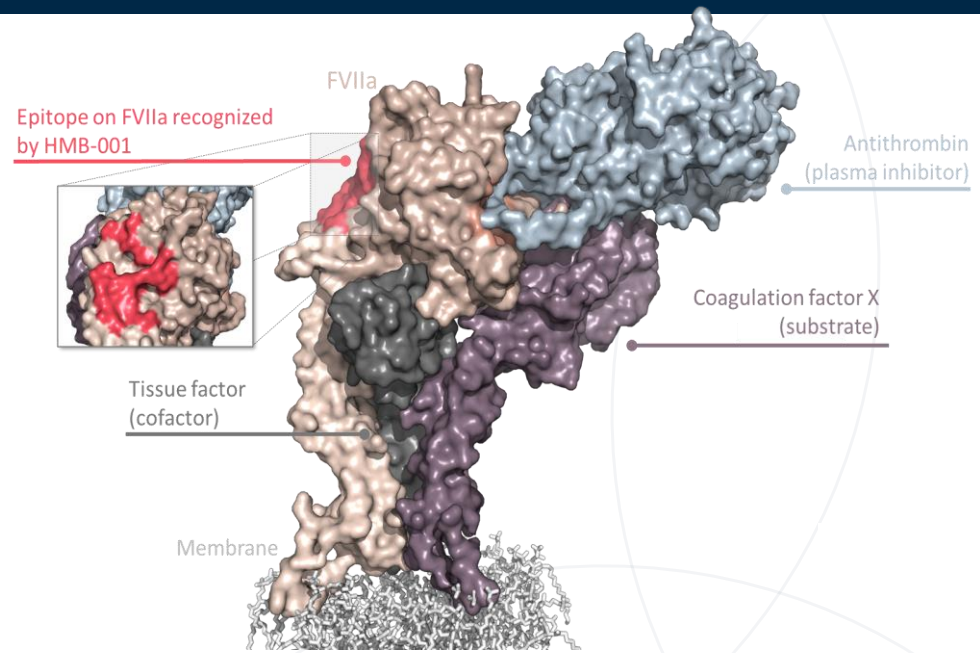
Anti-FVIIa binding arm of HMB-001 does not influence FVIIa activity



Study design:
- *In vitro* assays were done to assess influence of anti-FVIIa binding arm of HMB-001 on the ability of FVIIa to activate FX or FVII in presence and in absence of tissue factor (TF) and/or phospholipid vesicles (PSPC) and inhibition of FVIIa by ATIII, in presence of heparin, and α2M

Conclusions:
- Anti-FVIIa arm of HMB-001 does not influence ability of FVIIa to activate FX and FVII
- While ATIII inhibition is retained; HMB-001 abrogates α2M inhibition of FVIIa

Crystal structure of FVIIa with anti-FVIIa Fab reveals basis for lack of HMB-001 influence on FVIIa activity



Study design:
- Crystal structure of the anti-FVIIa Fab of HMB-001 was solved in complex with FVIIa bound to soluble fragment of tissue factor
- Crystal structure overlayed with computational models of FVIIa bound to FX or Antithrombin

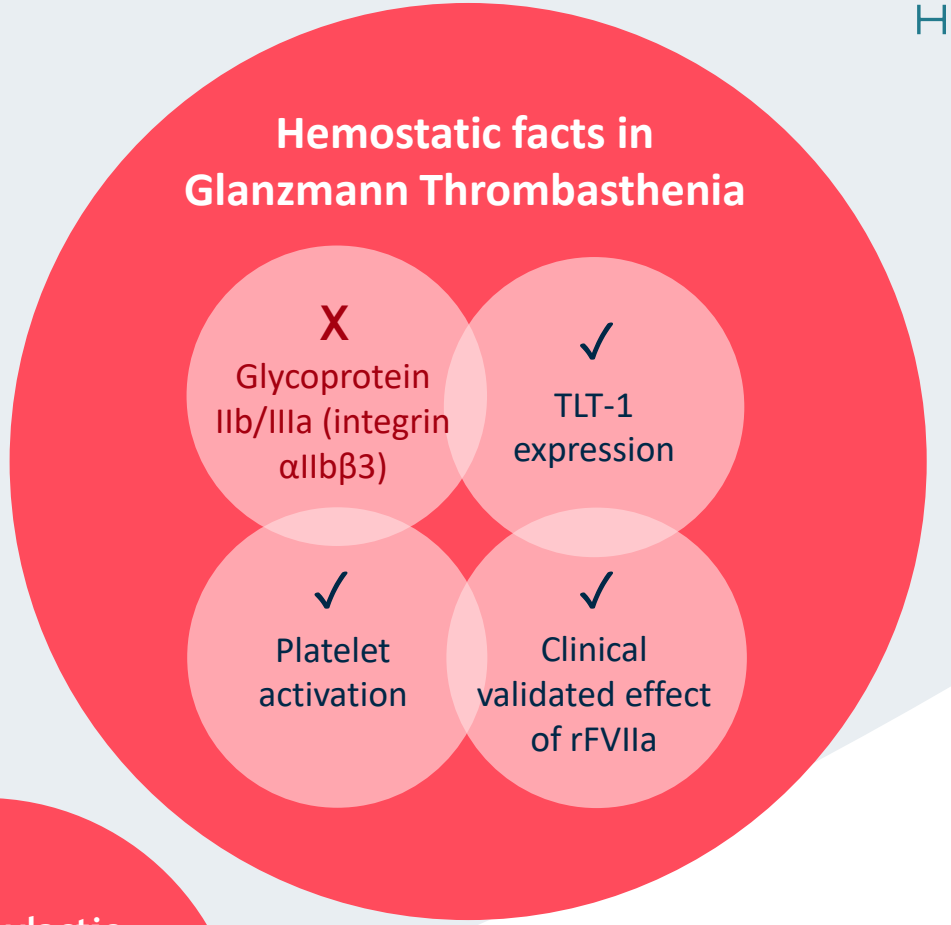
Conclusion:
- Binding epitope of anti-FVIIa arm of HMB-001 on FVIIa is distant from substrate, cofactor and inhibitor recognition epitopes on FVIIa as well as the FVIIa active site

Glanzmann Thrombasthenia | Definition

Cause
- Deficiency of Glycoprotein IIb/IIIa → Abnormal platelet aggregation → Recurring bleeding events

Affected Population
- Autosomal recessive rare bleeding disorder
- Females and Males
- Children and adults

Unmet need and Standard of Care
- Blood transfusions – red cells and platelets
- Recombinant factor VIIa for acute bleeds
- Bone marrow transplantation



No prophylactic treatment available

All available treatments are merely reactive

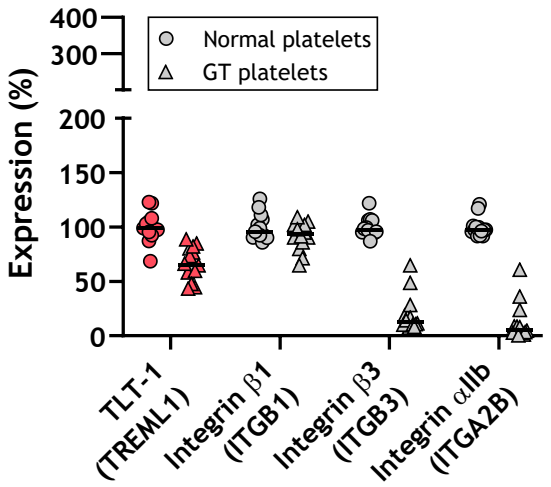
Median Prevalence
1:400,000

Approximately
18,500
patients worldwide

HMB-001 | Glanzmann Thrombasthenia

TLT-1 is present in GT platelets

Presence of key receptors

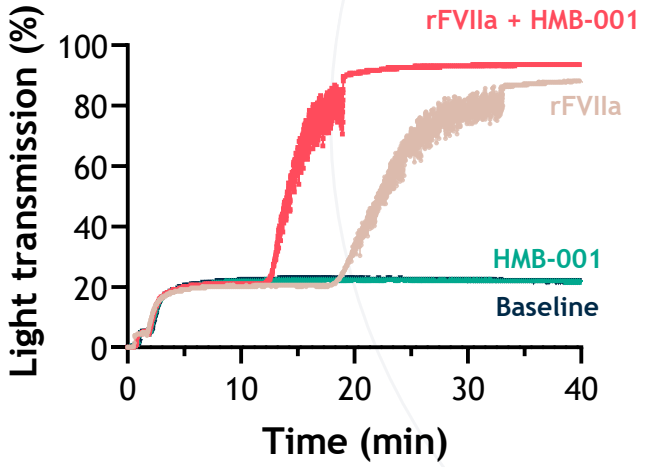


Study design:
- Analysis of total platelet lysates by MS

Conclusions:
- TLT-1 is expressed on platelets from patients with GT - around 67% of normal control subjects

HMB-001 potentiates rFVIIa activity in platelet aggregation assay in GT platelets

Aggregation of GT platelets

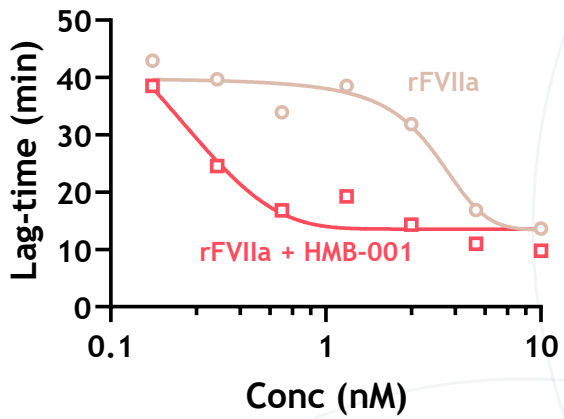


Study assay:
- Platelet aggregometry assay
- 10 nM rFVIIa, 10 nM HMB-001, 10 nM rFVIIa+10nM HMB-001

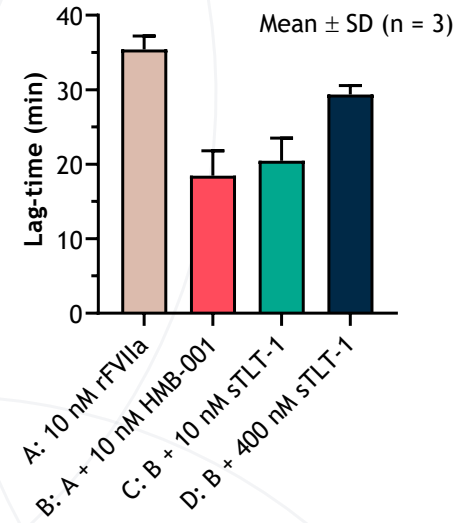
Conclusions:
- HMB-001 potentiates rFVIIa activity in GT platelets

Potentiation of rFVIIa activity by HMB-001 is dose-dependent and TLT-1-dependent

Dose-response



Effect of sTLT-1 on platelet aggregation lag-time



Study assay:
- Platelet aggregometry assay
- rFVIIa or rFVIIa:HMB-001 (1:1 co-formulation)

Conclusions:
- Dose-response of potentiation is established
- Potentiation can be reversed by adding excess sTLT-1

Conclusions

HMB-001 is a novel bispecific antibody that binds FVIIa and TREM-like transcript (TLT)-1 receptor on activated platelets with its two respective arms

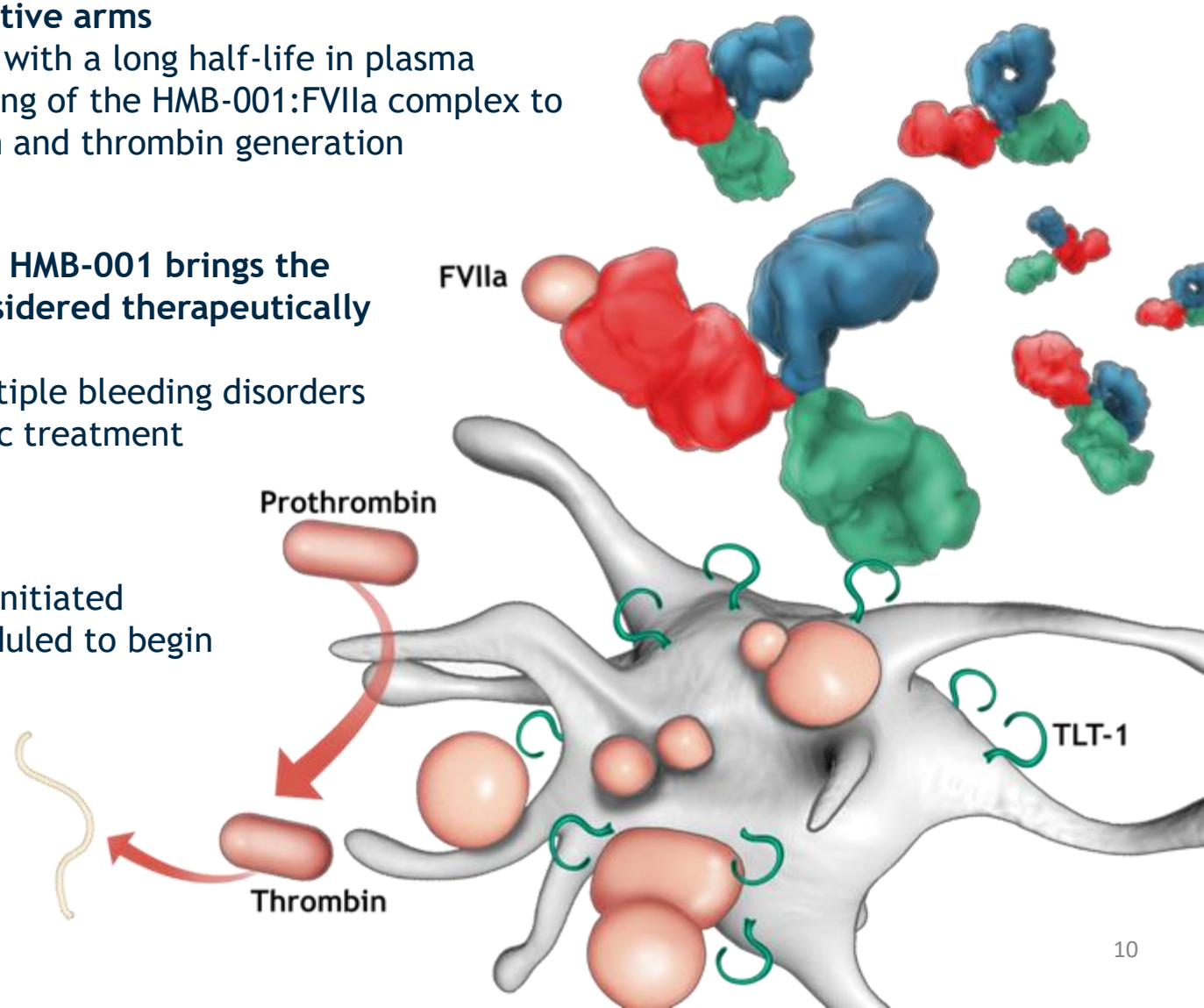
- Accumulates endogenous FVIIa by endowing FVIIa with a long half-life in plasma
- Potentiates activity of FVIIa through TLT-1 targeting of the HMB-001:FVIIa complex to activated platelets to promote local FX activation and thrombin generation

Combining accumulation and activity potentiation, HMB-001 brings the activity of endogenous FVIIa to levels that are considered therapeutically effective based on clinical experience with rFVIIa

- HMB-001 may have broad applicability across multiple bleeding disorders enabling subcutaneous and long-term prophylactic treatment

HMB-001 is in CTA/IND enabling development

- A series of natural history studies have been initiated
- Phase 1/2 clinical trial in GT patients is scheduled to begin in late 2022



Thank You

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