Interim Results of the First-in-Human Investigation of HMB-001 for Prophylactic Management of Glanzmann Thrombasthenia

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*Phase I was conducted at Richmond Pharmacology Ltd (RPL)

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Conflict of Interest

Dr. Sivapalaratnam reports the following conflicts of interest:

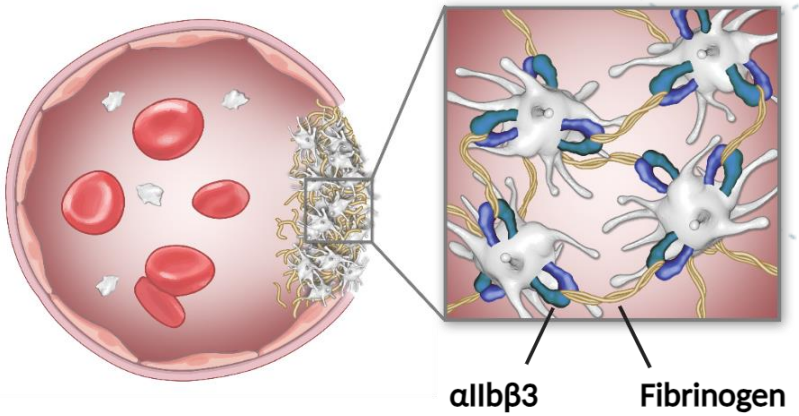
- Consulting for Hemab Therapeutics Sanofi and Chugai Pharmaceuticals

Glanzmann Thrombasthenia

- Rare and severe bleeding disorder
- Median prevalence: 1 in 450,000
- Deficiency of integrin αIIbβ3,* a platelet receptor essential for platelet aggregation
- Frequent bleeding events: 87% of patients reported having had a bleed in the past week (average of 3.5 bleeds in the past week)[1]
- Impact: 80% missed school or work due to bleeding or bruising. 70% reported fatigue[1]
- No therapies approved for prophylactic treatment; available options are impractical due to short half-life and frequent IV requirements

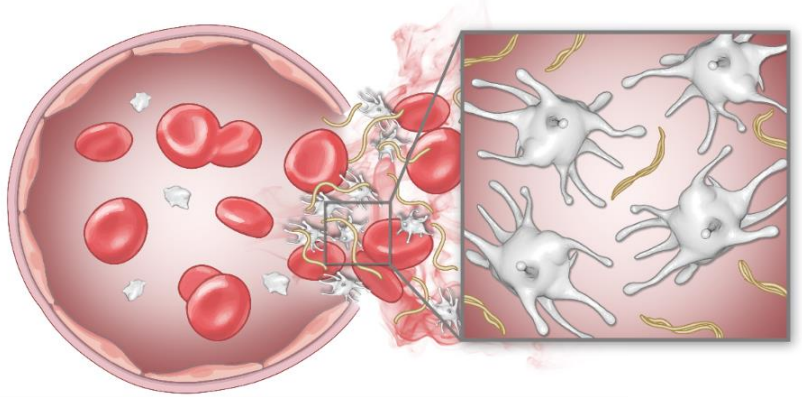
Healthy Platelet Aggregation

Fibrinogen binding to αIIbβ3 is required for normal platelet aggregation and haemostasis



Glanzmann Thrombasthenia

Deficiency of αIIbβ3 results in lack of fibrinogen-mediated bridging of platelets and a bleeding phenotype

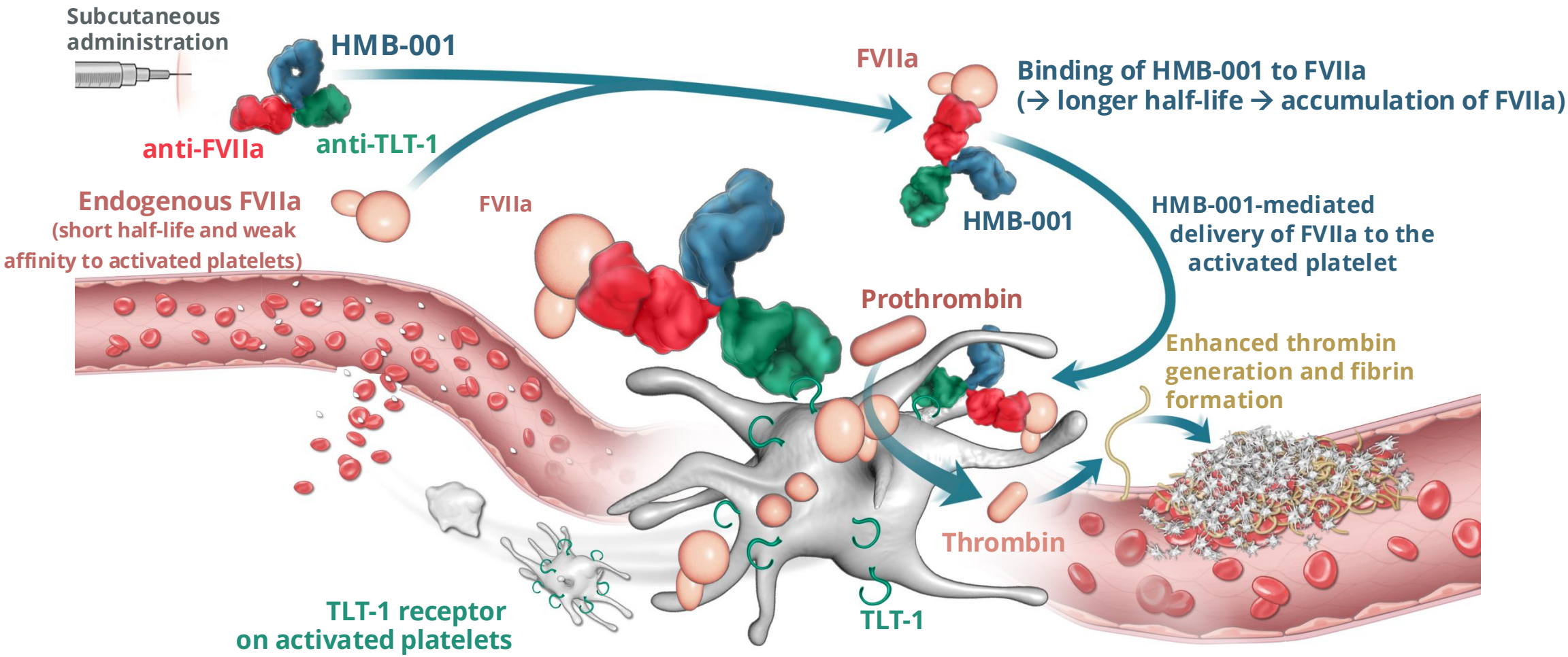


* Also known as glycoprotein (GP) IIb/IIIa

[1]Khair K. Glanzmann's 360 Study [Speaker Abstracts]. *Haemophilia* (2023), 29: 5-13.2.

HMB-001 | A Novel Bispecific Antibody Targeting FVIIa & TLT-1

HMB-001 binds and accumulates endogenous FVIIa and, following vessel lesion, localises FVIIa to the surface of activated platelets

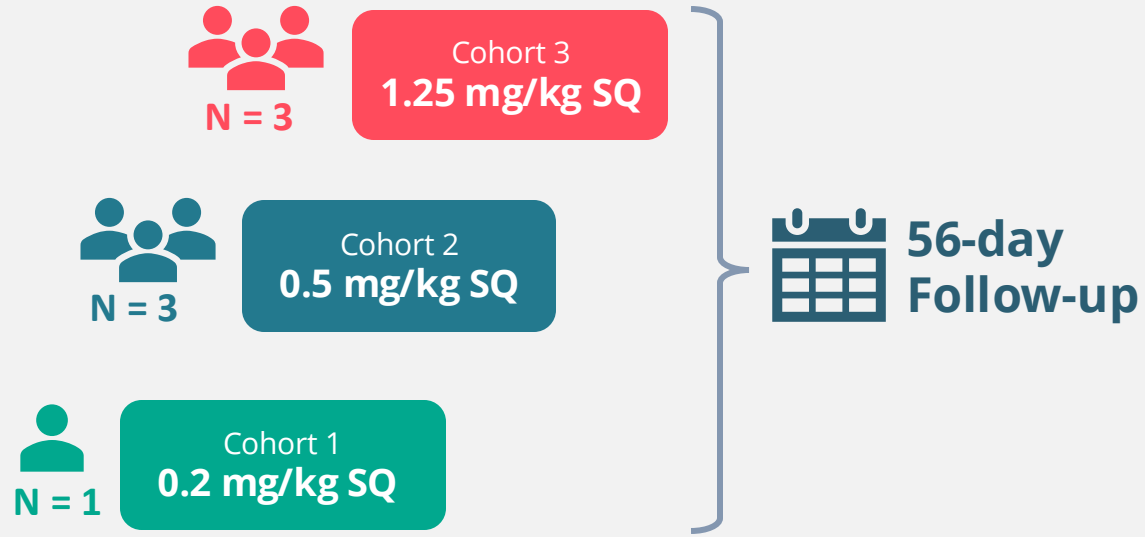


[1]Gandhi PS, Zivkovic M, Østergaard H, et. al., (2024) A bispecific antibody approach for the potential prophylactic treatment of inherited bleeding disorders. Nature Cardiovascular Research.

HMB-001 Phase 1/2 Study

Dose-escalation study in three parts

Phase 1
Single Ascending Dose Study



Phase 2
Multiple Ascending Dose Study

Multiple Dose Cohorts

3 months treatment

Phase 2b
Extension Study

Recommended Phase 2b Dose/Regimen TBD

9 months treatment

12 months of treatment

Study Objective:

Evaluate pharmacokinetics, pharmacodynamics (FVIIa assay – Stago clot activity assay, total FVII(a) - ELISA antigen assay), safety, and tolerability, aiming to identify the optimal dosing levels and intervals for future studies in Phase 2.

Interim HMB-001 Phase 1 Study Results
Demographics & baseline characteristics

Study inclusion criteria:

- Definitive Glanzmann Thrombasthenia diagnosis
- Males and females
- Age 18 to 65 years

	0.2 mg/kg (N=1)	0.5 mg/kg (N=3)	1.25 mg/kg (N=3)
Age, mean (range)	33.0	32.0 (27–41)	47.7 (46–49)
Sex, n (%)			
Female	1 (100.0)	2 (66.7)	3 (100.0)
Male	-	1 (33.3)	-
Childbearing potential, n (%)	1 (100.0)	2 (66.7)	3 (100.0)
Race, n (%)			
Asian	1 (100.0)	2 (66.7)	3 (100.0)
White	-	1 (33.3)	-

SD: standard deviation

Data extract: 16Nov2023. Data are from an ongoing study and are not considered final.

Interim HMB-001 Phase 1 Study Results
Safety & tolerability (Part A, N=7)

Adverse Events (AEs)*

- No AEs/SAEs related to HMB-001
- Majority of AEs mild or moderate severity
- No dose-limiting toxicities
- No thromboembolic events

Coagulation

- No clinically significant changes in fibrinogen and APTT
- Transient (~10%) change in platelet count over first 2 weeks*
- No apparent change in D-dimer at 0.2 and 0.5 mg/kg doses. Temporary increase in D-dimer at 1.25 mg/kg, suggesting a potential dose-related effect. This increase remains within clinically acceptable parameters and is not associated with any clinical signs or symptoms.

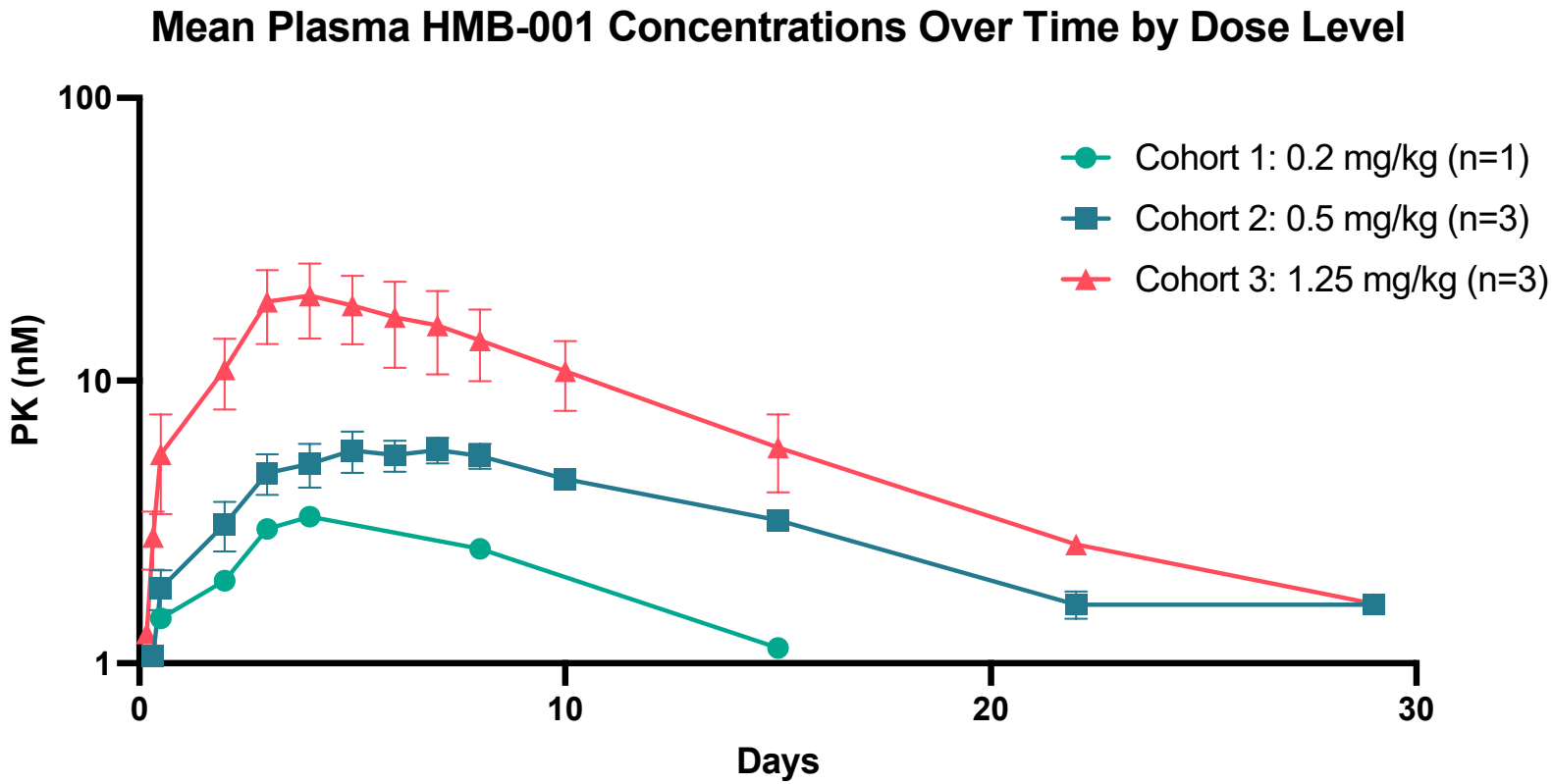
Data extract: 16Nov2023. Data are from an ongoing study and are not considered final.

*All platelet count results were >130 10^9/L

Interim HMB-001 Phase 1 Study Results

Pharmacokinetics (PK) concentration after single dose

- Dose proportionality
- Half-life supports dosing every 2 weeks or less frequently



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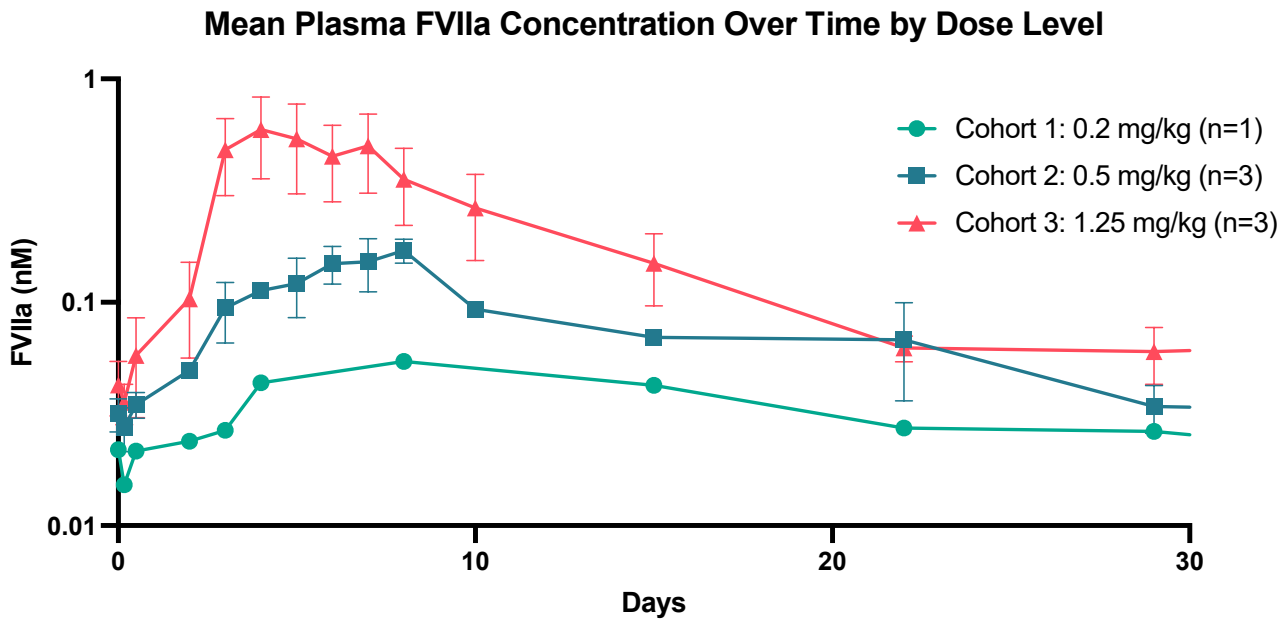
Interim HMB-001 Phase 1 Study Results

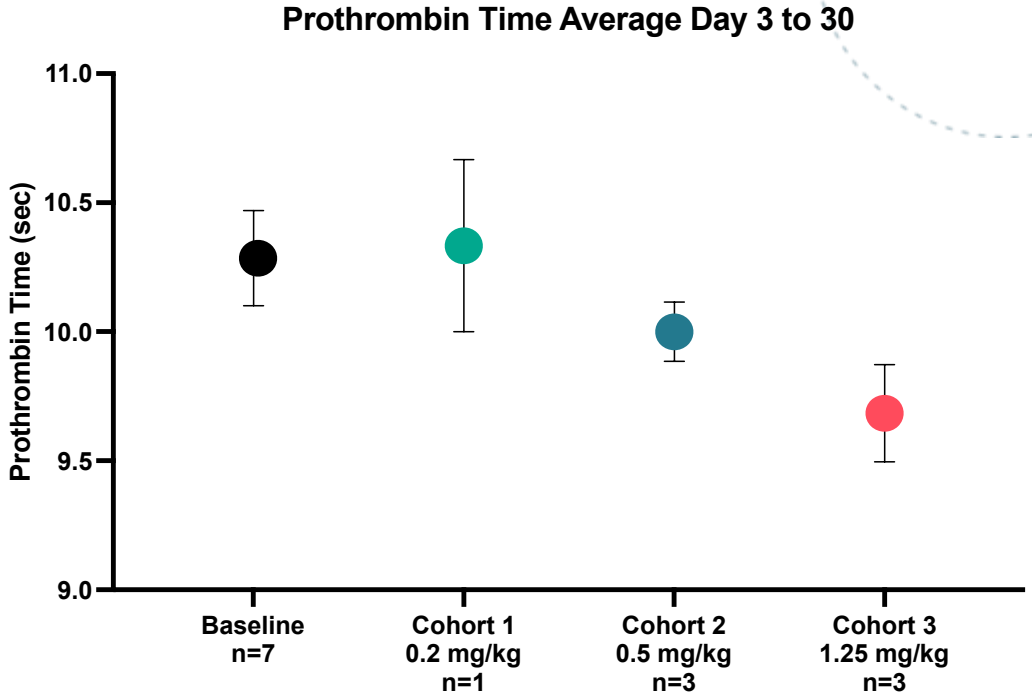
Pharmacodynamics (PD): FVIIa & prothrombin time changes after single dose

- Dose-dependent accumulation of endogenous FVIIa
- Durability of FVII/FVIIa increase proportional to HMB-001 PK



FVIIa assay - Stago clot activity assay

- Dose-dependent decrease in prothrombin time



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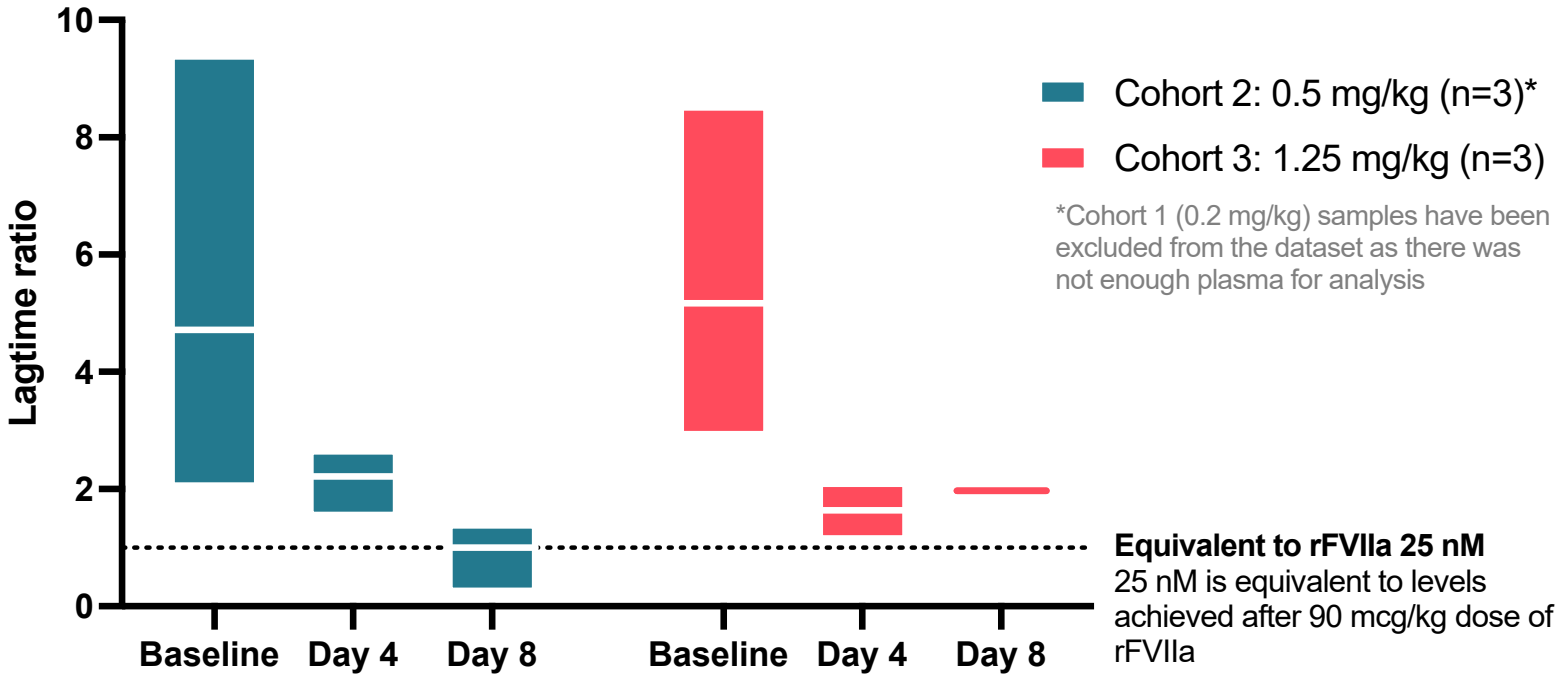
Interim HMB-001 Phase 1 Study Result

Exploratory thrombin generation and HMB-001 mediated potentiation

- Results from the PRP-TG assay indicate enhancements mediated by targeted TLT-1 binding could achieve at least a 40-fold potentiation.

Lagtime Ratio: Measured value in patient plasma pre and post HMB-001 versus value obtained in the presence of 25nM rFVIIa (mean, max, min)



*Cohort 1 (0.2 mg/kg) samples have been excluded from the dataset as there was not enough plasma for analysis

Equivalent to rFVIIa 25 nM
25 nM is equivalent to levels achieved after 90 mcg/kg dose of rFVIIa

Exploratory Adapted Thrombin Generation Assay

- Baseline and post dose samples from patients
- Platelet poor plasma reconstituted with pooled washed treated (activated and GT like) platelets
- Measured using Calibrated Automated Thrombogram method
- Lagtime refers to the duration required for a blood sample to initiate clotting

HMB-001 Phase 1/2 Study

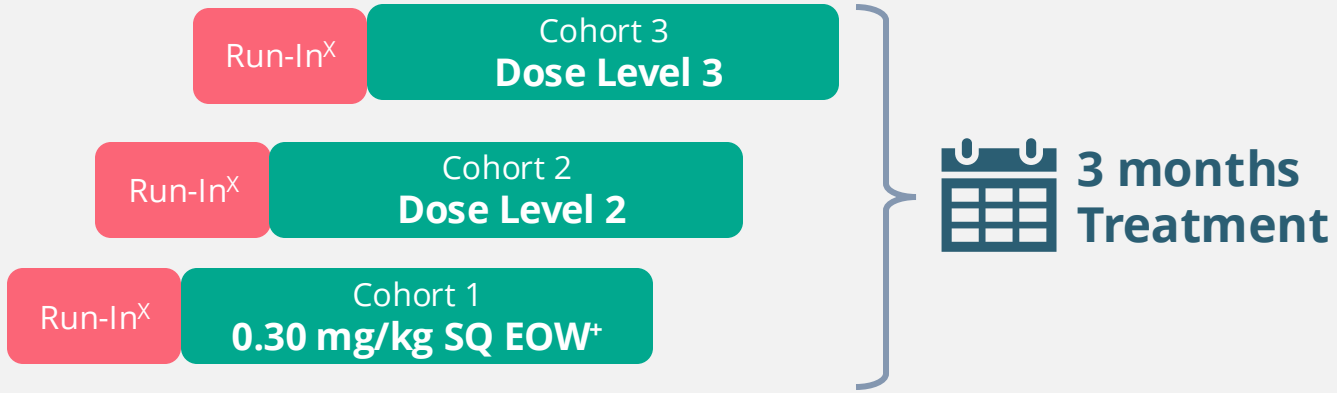
Phase 2 is now enrolling

Phase 1
Single Ascending Dose Study

- 7 patients
- 3 dose cohorts
- 56 days follow-up

Phase 2
Multiple Ascending Dose Study

Open-Label study of Safety, PK, PD, and ABR*



Administered SQ weekly, every two weeks, or monthly.
Number of cohorts, dose levels/regimen for patient to change per adaptive features in protocol

Phase 2b
Extension Study

Recommended Phase 2 Dose/Regimen TBD

9 months Treatment

*Annualized Bleeding Rate, Annualized Treated Bleeding Rate
[X] Comprehensive recording of bleeding incidents throughout the Run-In period along with a 12-Month retrospective data compilation on bleeding events
[+]Every other week

HMB-001 Phase 1 Study Results
Interim conclusions to date

- **Favorable safety and tolerability profile**; no HMB-001 related adverse events and no thrombotic events observed
- Linear pharmacokinetic (PK) profile and half-life of ~10 days; supportive of **dosing every 2 weeks or less frequently**
- Pharmacodynamic data showed **proof of mechanism of action**:
  - Dose-dependent **accumulation of endogenous FVIIa** with associated decreases in prothrombin time
  - **Enhanced thrombin generation** parameters validate the potentiation of FVIIa activity mediated by HMB-001 in the presence of activated platelets.
- Phase 2 will continue examining safety/tolerability and efficacy as assessed by bleeding event frequency and severity

Preliminary findings from the initial phase of this Phase 1/2 study support the continued development of HMB-001 as a potential prophylactic treatment for Glanzmann Thrombasthenia.

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Acknowledgements

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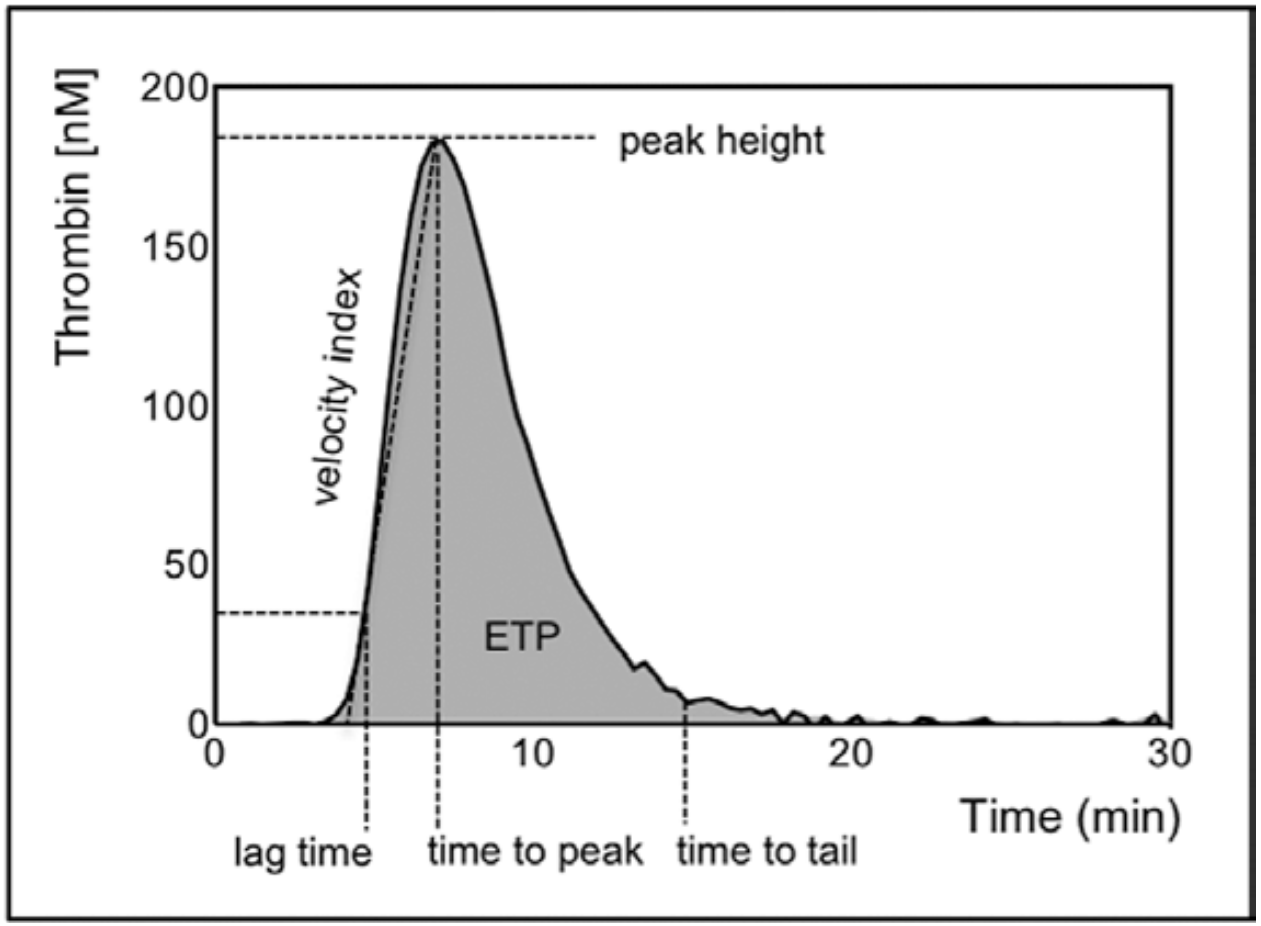
- The authors thank the study participants, their families, the investigators and study site personnel



Thrombin generation curve and parameters. Example of a thrombin generation curve obtained by means of the CAT method in a healthy individual. The main parameters derived from the curve are: (a) the lag time (the time until 1/6 of the peak height is reached), which approximates the clotting time, (b) the peak height or maximum amount of thrombin formed, (c) the endogenous thrombin potential or area under the curve, corresponding to the total amount of thrombin formed, and (d) the time to tail or the time until the end point of thrombin generation.