Hämophilie-Zentrum am
Universitätsklinikum des Saarlandes

15. Hämophilie-Symposium Homburg

Dr. Sabine Heine

Samstag 19.11.2022

Hämophilie-Zentrum am
Universitätsklinikum des Saarlandes

Aktuelle Forschung zur Therapie der Hämophilie – Nicht-Faktor-Präparate

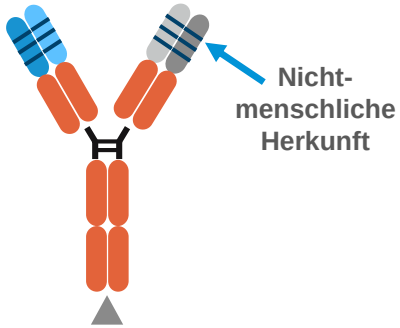
Dr. Sabine Heine

Emicizumab – bispezifischer monoklonaler Antikörper

- Emicizumab ist ein **humanisierter bispezifischer, monoklonaler Antikörper**

- Emicizumab **bindet FIX/FIXa und FX/FXa** und **übernimmt die Funktion von FVIIIa**, um eine physiologische Blutgerinnung zu ermöglichen

- Vorteile humanisierter Antikörper
  - niedrige Immunogenitätsrate
  - lange Plasmahalbwertszeiten
  - hohe subkutane Bioverfügbarkeit
  - In anderen Indikationen seit Jahren etabliert



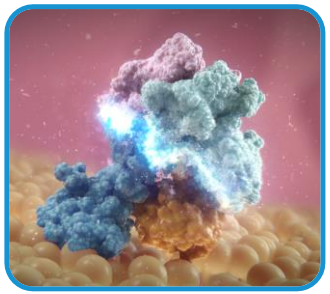
Humanisiert
(Suffix: -zumab)

Der größte Teil der Aminosäuresequenz ist von einer menschlichen DNA-Sequenz abgeleitet, mit Ausnahme der CDRs, die auf einer DNA-Sequenz nicht-menschlichen Erbguts basieren

Slide Courtesy of Roche Pharma

Wirkmechanismus von Emicizumab im Vergleich zu FVIII

Faktor VIII



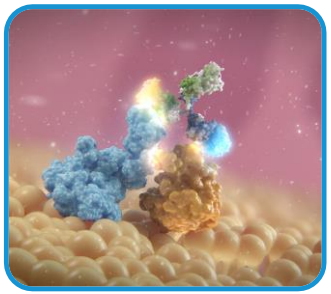
Wenn genügend FVIII vorhanden ist, bindet FVIII an Thrombin, um aktiviert zu werden (FVIIIa)

FVIIIa bindet dann an FIXa, um einen Tenasekomplex auf der Thrombozyten-Oberfläche zu bilden

Der Komplex bindet dann an FX, um dessen Aktivierung durch FIXa zu ermöglichen

Dieser Teil der Gerinnungskaskade **kann ohne FVIII nicht stattfinden**

Emicizumab



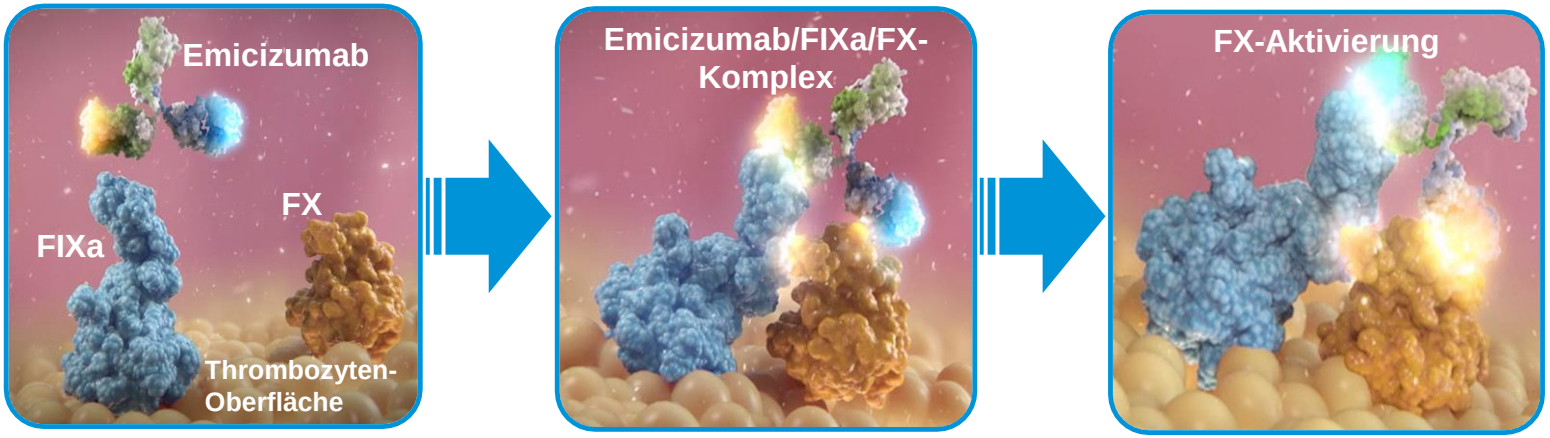
- Als bispezifischer, monoklonaler Antikörper **übernimmt Emicizumab die hämostatische Funktion von FVIIIa** durch **Bindung an FIXa und FX**

➢ Dadurch kann die **Gerinnungskaskade normal** weiterlaufen

- Hemmkörper gegen FVIII können Emicizumab weder binden noch neutralisieren und haben daher keinen Einfluss auf die hämostatische Aktivität von Emicizumab

Slide Courtesy of Roche Pharma

Wirkmechnismus von Emicizumab



Als bispezifischer monoklonaler Antikörper **übernimmt Emicizumab die Funktion von FVIIIa**:

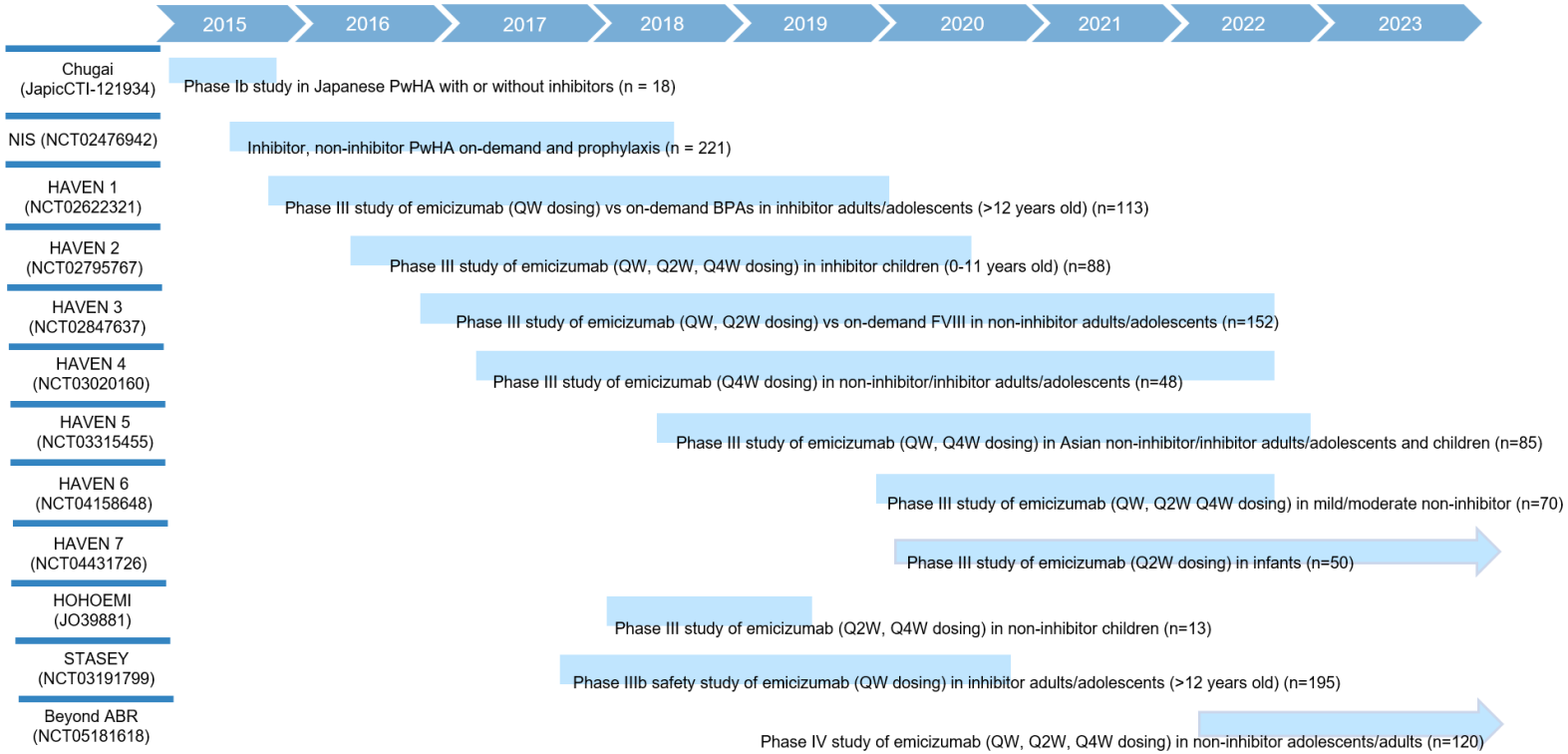
Emicizumab bindet sowohl an FIXa als auch an FX und ermöglicht die **Aktivierung von FX zu FXa durch FIXa.**

Das löst die **Aktivierung der restlichen Gerinnungskaskade** aus und stellt die **physiologische Gerinnung** wieder her.

Slide Courtesy of Roche Pharma

Klinisches Entwicklungsprogramm von Emicizumab

Emicizumab clinical development program[1]

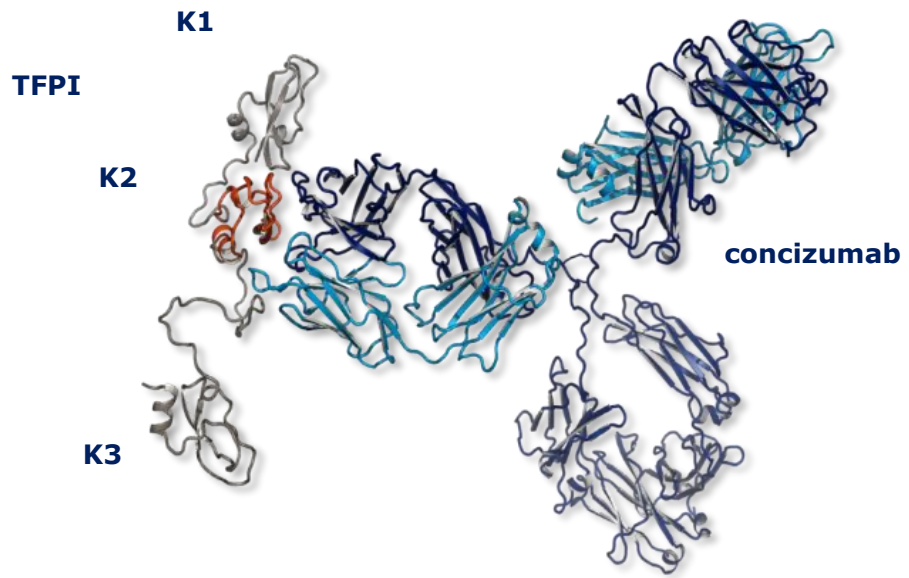


ABR, annualised bleeding rate; NIS, non-interventional study; PwHA, people with haemophilia A; QW, once weekly administration; Q2W, 2-weekly administration; Q4W, 4-weekly administration

1. https://clinicaltrials.gov/ct2/home (accessed January 2022)

Slide Courtesy of Roche Pharma

Concizumab



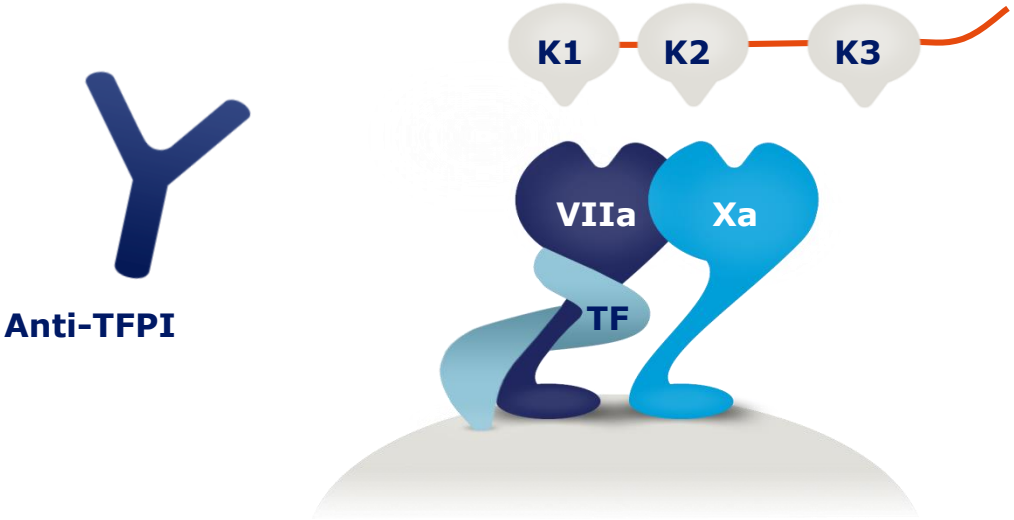
- Humanisierter IgG_4 Antikörper gegen TFPI (tissue factor pathway inhibitor)
- Hohe Affinität für die Kunitz-2 Domäne von of TFPI (K_D~25 pM)
- Die Kunitz-2 Domäne (K2) von TFPI bindet an FXa

Hilden I, et al. *Blood* 2012;119:5871–8.

Slide Courtesy of Novo Nordisk

Concizumab

Ein monokloner Antikörper gegen die K2-Domäne von TFPI neutralisiert den inhibierenden Effekt von TFPI



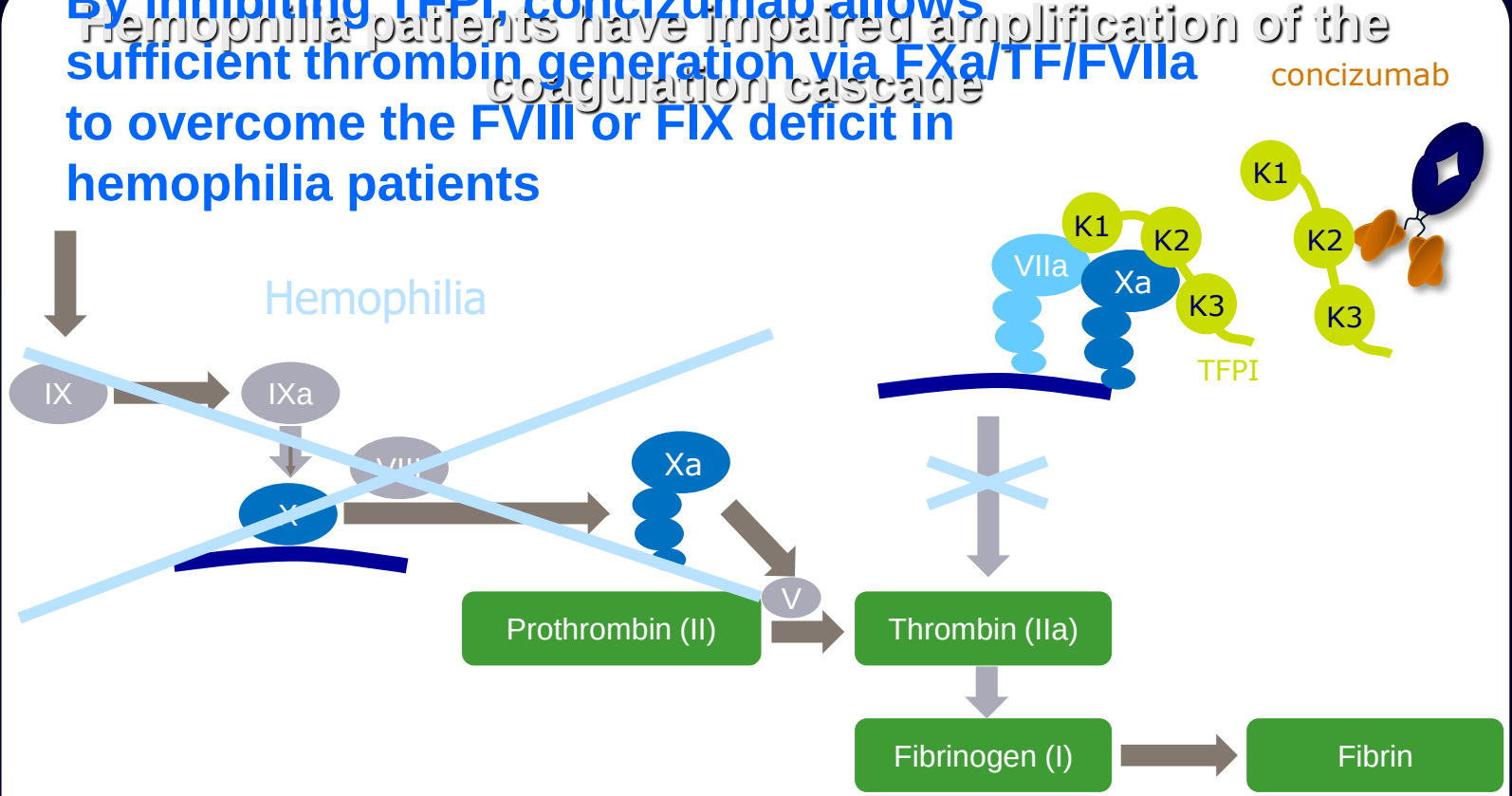
Ein monoklonaler Ak gegen K2 blockiert TFPI und ermöglicht so ein Fortschreiten der Initiierungsphase
→ Ein Mangel an FVIII/IX-abhängiger Thrombingenerierung wird dadurch kompensiert

Adapted from Hilden I, et al. *Blood* 2012;119:5871–8.

Slide Courtesy of Novo Nordisk

Concizumab

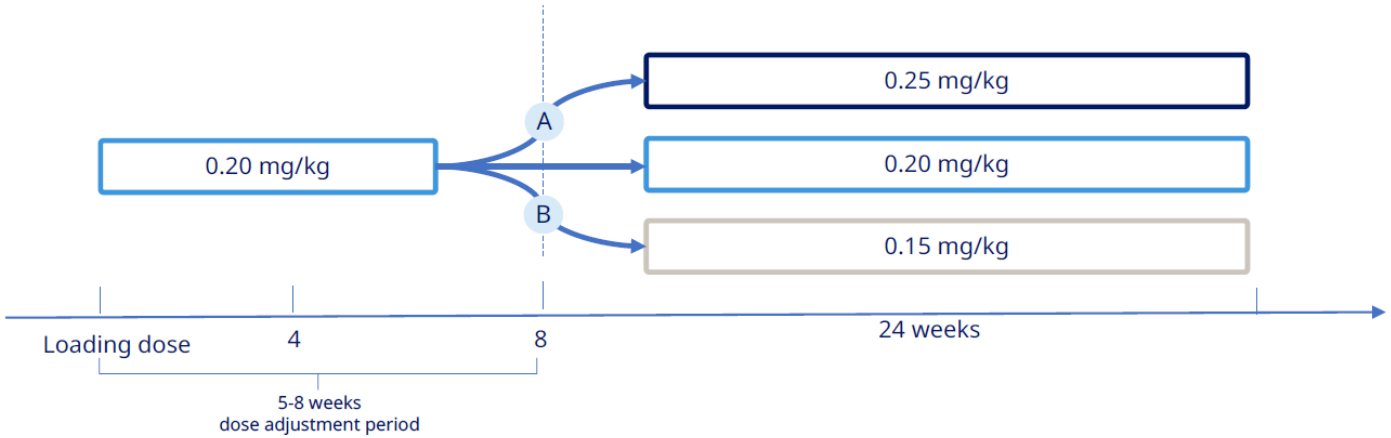
By inhibiting TFPI, concizumab allows sufficient thrombin generation via FXa/TF/FVIIa to overcome the FVIII or FIX deficit in hemophilia patients



Slide Courtesy of Novo Nordisk

Concizumab
Explorer 7 Study

explorer7 dosing regimen



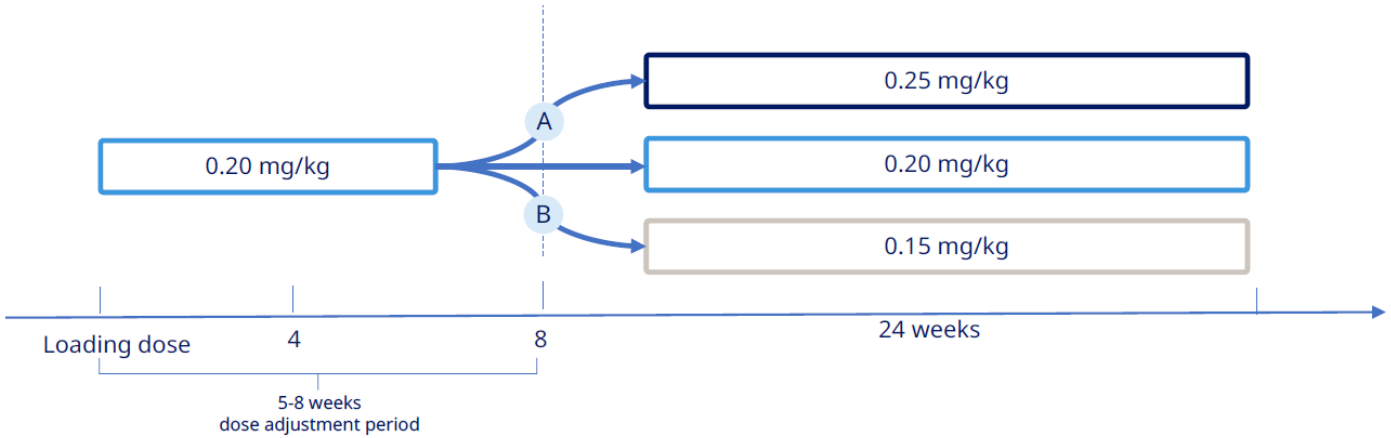
1 mg/kg loading dose followed by **0.2 mg/kg QD** and potential dose adjustment based on week 4 PK

- A Patients <200 ng/mL **increase the dose to 0.25 mg/kg**
- B Patients >4000 ng/mL **decrease the dose to 0.15 mg/kg**

PK, pharmacokinetics; QD, once daily
NCT04083781

Concizumab
Explorer 7 Study

explorer7 dosing regimen



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PK, pharmacokinetics; QD, once daily
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Concizumab
Explorer 7 Study

explorer7 key endpoints

Primary endpoint:
- The number of treated spontaneous and traumatic bleeding episodes (estimated mean ABR)

Secondary endpoints:
- Change in SF-36v2 bodily pain
- Change in SF-36v2 physical functioning

Supportive secondary endpoints

Efficacy:
- Number of treated spontaneous bleeding episodes
- Number of treated spontaneous and traumatic joint bleeds
- Number of treated spontaneous and traumatic target joint bleeds

Safety:
- Number of adverse events (including thromboembolic events, hypersensitivity-type reactions and injection site reactions)

ABR, annualised bleeding rate (treated); SF-36v2, 36-Item Short-Form Health Survey
NCT04083781

Concizumab
Explorer 7 Study

explorer7 conclusions

- Overall median ABR on concizumab PPX was 0
- Concizumab PPX was effective in reducing ABR compared with no PPX in HAwI/HBwI
- Estimated mean ABR was 1.7 for concizumab PPX and 11.8 for no PPX

- Concizumab appeared to have a safe and well-tolerated profile in HAwI/HBwI
- No thromboembolic events were reported after treatment restart
  - Prior to the treatment pause, one event of non-fatal renal infarct was reported

- Concizumab exposure was stable over time
- Free TFPI was suppressed and thrombin generation potential normalised

- Positive trend was observed for all SF-36v2 domains
- There was no significant difference between the two randomised arms for the key secondary endpoints (bodily pain and physical functioning)

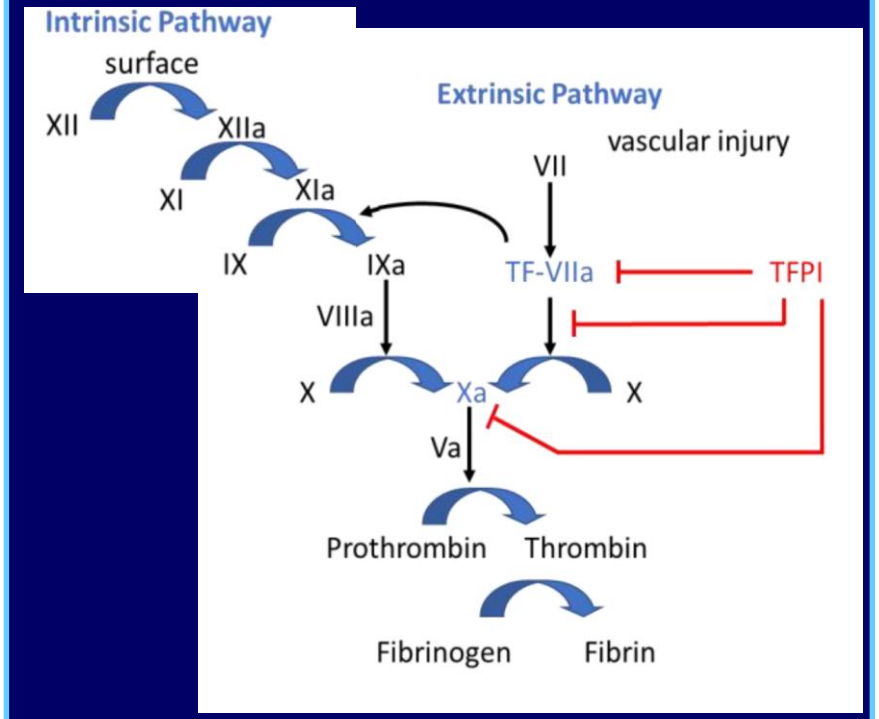
ABR, annualised bleeding rate (treated); HAwI, haemophilia A with inhibitors; HBwI, haemophilia B with inhibitors; PPX, prophylaxis; SF-36v2, 36-Item Short-Form Health
NCT04083781

ISth 2022

Victor Jiménez-Yuste *et al.* ISTH 2022

Marstacimab

- TFPI is a Kunitz-type serine protease inhibitor that acts as a negative regulator of coagulation
- It is the primary inhibitor of the extrinsic pathway complex TF–FVIIa
- By binding to the active site of FVIIa, TFPI indirectly inhibits the activation of FX
- Activation of FX is an essential step in the generation of thrombin and the subsequent conversion of fibrinogen to insoluble fibrin



Adapted from: Smith et al. 2015;[2] Maroney and Mast 2015;[3] Lwaleed and Bass 2006;[4] and Ragni 2017.[5]

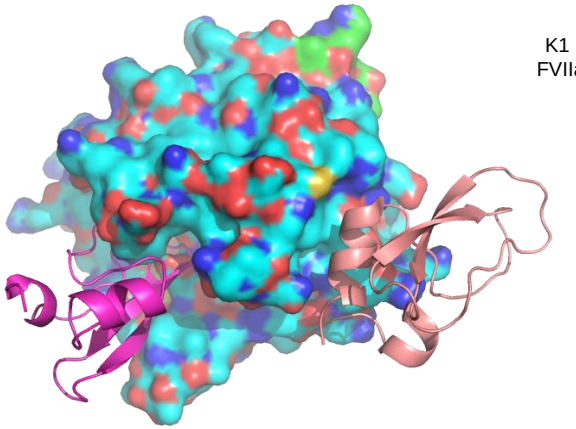
Slide Courtesy of Pfizer

Marstacimab
BASIS

Marstacimab is an inhibitor of tissue factor pathway inhibitor (anti-TFPI)

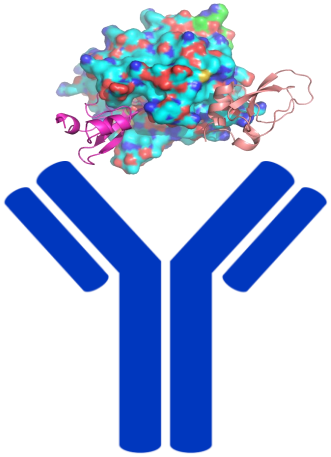
Human monoclonal antibody, specific for Kunitz 2 domain of TFPI

K2 domain:
FXa binding



K1 domain:
FVIIa binding

K3 domain: Not a known serine protease inhibitor
K3/C-terminal basic region: Binds heparin, HSPG, LRP



Slide Courtesy of Pfizer

Marstacimab

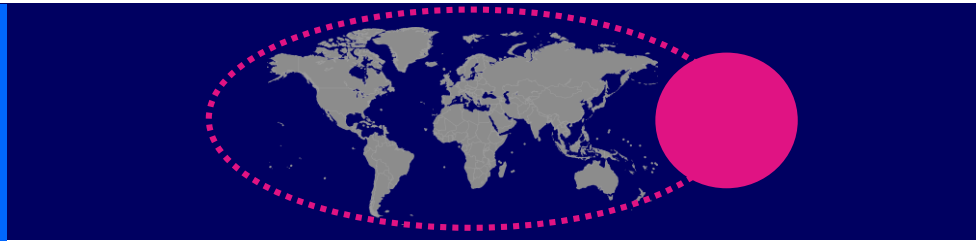
An open-label study in adolescent and adult with severe hemophilia A or B with or without inhibitors comparing standard treatment to marstacimab prophylaxis

Key Inclusion Criteria	Treatment	Key Primary Outcomes
• Male subjects ages 12-74 years with severe hemophilia A or moderately severe to severe hemophilia B with a minimum weight of 30 kg at screening	• 300 mg SC loading dose followed by 150 mg SC QW • Participants will be assigned to treatment with marstacimab after a 6-month observation period on their current hemophilia regimen	• ABR of treated bleeding events through the observational phase (6 months) and the active treatment phase (12 months) for a total of approximately 18 months

Estimated study completion:
Sep 2024

Estimated N = 145

63 sites

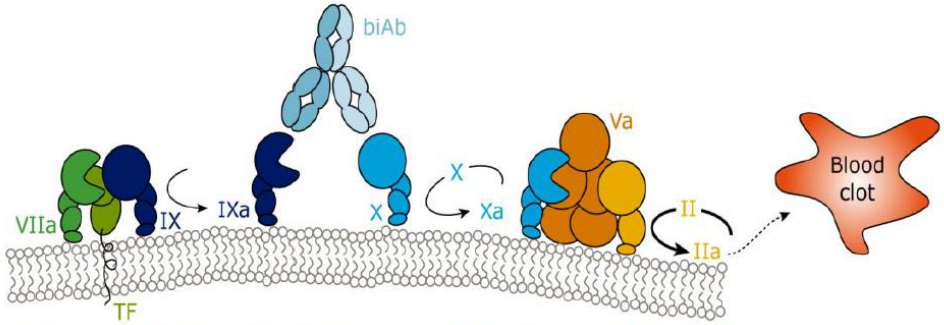


Slide Courtesy of Pfizer

Mim8

Mim8 mechanism of action

STRONG ACTIVITY AT SITE OF BLEEDING

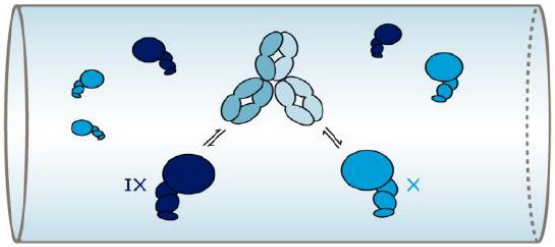


FIX ARM PROPERTIES
STIMULATION

FX ARM PROPERTIES
EXCHANGE

- Membrane localisation of the Mim8-FIXa-FX complex
- Facilitated delivery of FX to FIXa
- Stimulation of the proteolytic activity of FIXa

MINIMAL ACTIVITY IN CIRCULATION



LONG HALF-LIFE
GOOD SAFETY

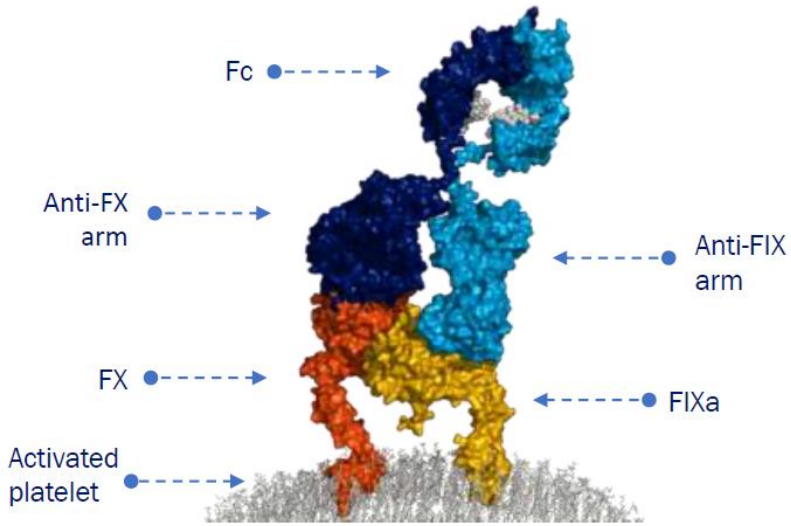
- Llittle binding to FIX and FX in solution

Slide Courtesy of Novo Nordisk

Mim8
Frontier1 MAD

Mim8 is a FVIIIa mimetic currently in clinical development for the treatment of haemophilia A

Mim8



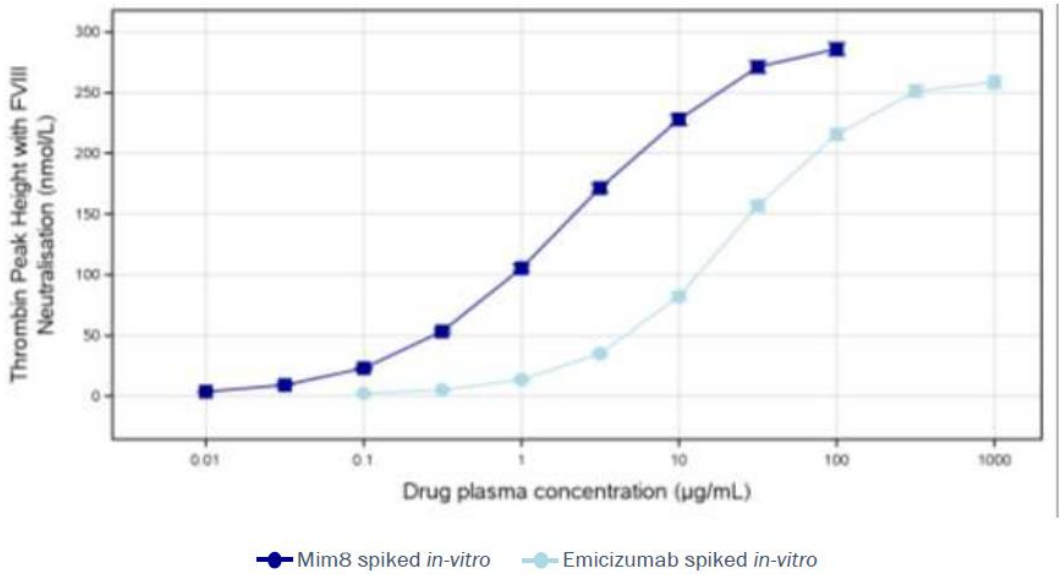
- Novel, next-generation FVIIIa mimetic
- Fully human IgG4 bispecific antibody
- Optimised to enhance the proteolytic activity of FIXa
- Weak binding to circulating FIX/FX to avoid activation of systemic coagulatic

Fc, fragment crystallisable; FIX, coagulation factor IX; FIXa, activated coagulation factor IX; FVIIIa, activated coagulation factor VIII; FX, coagulation factor X; IgG, immunoglobulin G.
Østergaard H et al. *Blood* 2021;138:1258–68.

Jerzy Windyga *et al.* ISTH 2022

Mim8
Frontier1 MAD

In-vitro spiking of Mim8 and emicizumab in HA-like plasma



HA, haemophilia A; SAD, single-ascending dose
Solid graphs represent HA-like plasma, made from normal plasma obtained from SAD cohort patients pre-dosing, spiked with different concentrations of Mim8 or emicizumab.

Jerzy Windyga *et al.* ISTH 2022

Mim8
Frontier1 MAD

Conclusions

- A dose-dependent increase in thrombin generation was observed in Mim8-treated patients, with Mim8 cohort 2 comparable to emicizumab cohort
- Thrombin generation results from patient samples correlated with *in-vitro* spiking
- Coagulation biomarkers did not indicate any safety signals following Mim8 treatment
- Combined with the overall safety and bleed data, these data support the further clinical development of Mim8 in patients with HA in phase 3 clinical trials

HA, haemophilia A

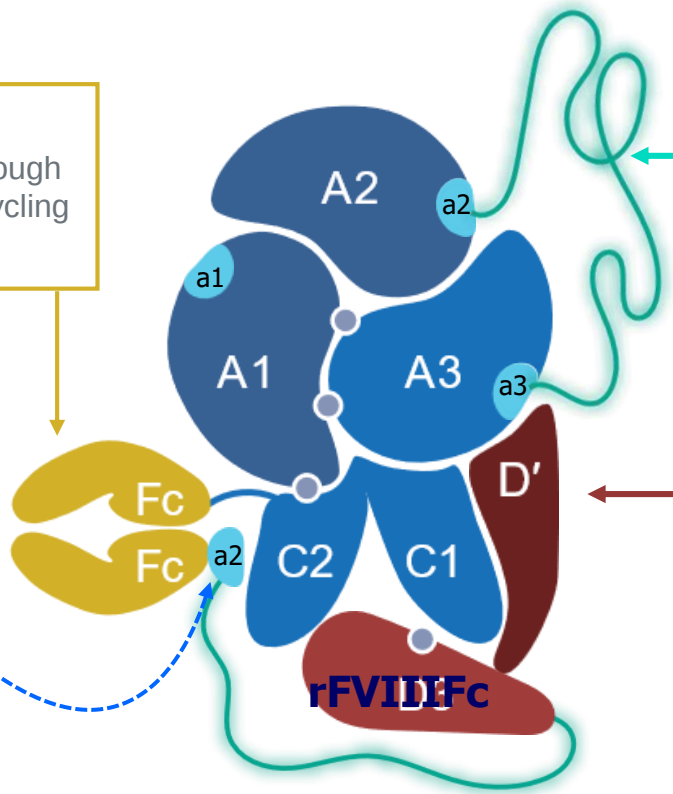
Efanesoctocog alfa (rFVIIIFc-VWF-XTEN; BIVV001)

Fc domain[1,2]

- Extends half-life through FcRn-mediated recycling pathway

Thrombin-cleavable linker[3]

- Enables release of D′D3 upon FVIII activation



XTEN®[a] polypeptides[4]

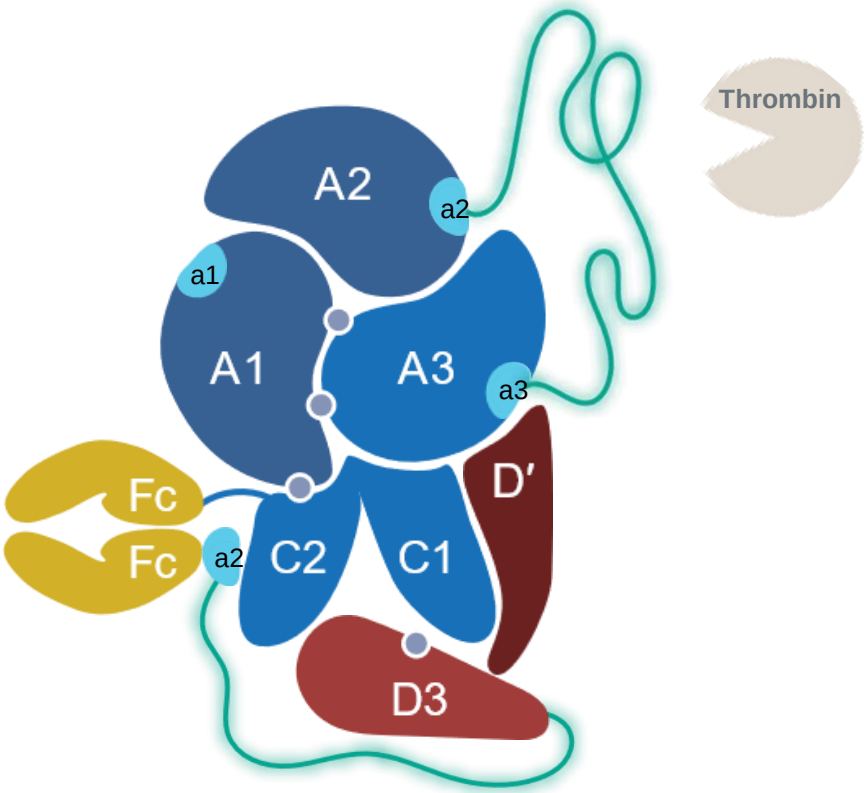
- Hydrophilic sequences comprising natural amino acids
- Provide protection, increase half-life

Covalent linkage to the D′D3 domain of VWF[3]

- Prevents binding to endogenous VWF, decoupling from VWF-mediated clearance
- Partial protection from degradation normally afforded by VWF

Slide Courtesy of Sobi / Adapted from Konkle et al NEJM 2020

Efanesoctocog alfa (rFVIIIFc-VWF-XTEN; BIVV001)

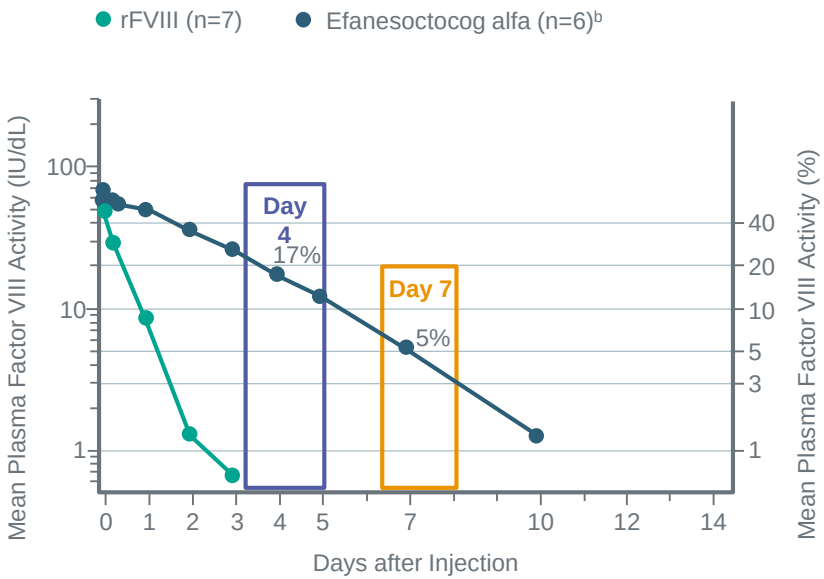


Activation of efanesoctocog alfa by thrombin results in a rFVIII-Fc fusion protein

Slide Courtesy of Sobi / Adapted from Seth Chhabra *et al* Blood 2020

Efanesoctocog alfa
EXTEN-A PK

EXTEN-A PK Results: Single 25 IU/kg dose[1,2]



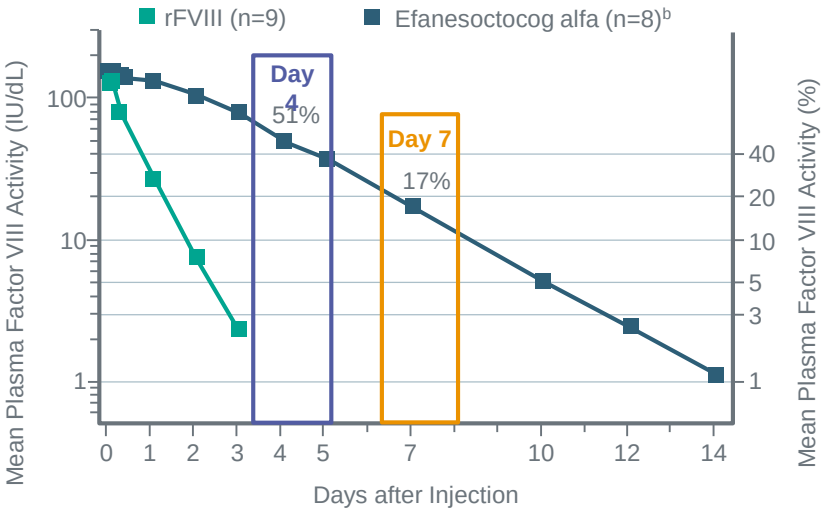
PK parameter[a,c]	25 IU/kg Efanesoctocog alfa (n=6)[b]	25 IU/kg rFVIII (n=7)	Mean ratio[d]
$t_{1/2}$, h	**37.61 (33.28–42.50)**	9.12 (6.24–13.33)	**4.13 (2.94–5.79)**
C_{max}, IU/dL	70.1 (49.7–98.9)	51.8 (43.3–61.9)	1.35 (1.04–1.77)
AUC_{0-inf}, h × IU/dL	4470 (3280–6080)	638 (495–822)	7.00 (5.78–8.48)
CL, mL/h/kg	0.56 (0.41–0.76)	3.91 (3.05–5.02)	0.14 (0.12–0.17)
IR, IU/dL per IU/kg	2.72 (1.95–3.80)	2.00 (1.60–2.50)	1.36 (0.98–1.89)

Efanesoctocog alfa mean (range) FVIII activity post-infusion was 17% (8-26%) at 4 days and 5% (2-10%) at 7 days

Slide Courtesy of Sobi

Efanesoctocog alfa
EXTEN-A PK

EXTEN-A PK Results: Single 65 IU/kg dose[1,2]



PK parameter[a,c]	65 IU/kg Efanesoctocog alfa (n=8)[b]	65 IU/kg rFVIII (n=9)	Mean ratio[d]
$t_{1/2}$, h	**42.54 (39.72–45.56)**	13.15 (10.89–15.87)	**3.24 (2.76–3.79)**
C_{max}, IU/dL	161 (142–183)	138 (117–162)	1.17 (1.09–1.25)
AUC_{0-inf}, h × IU/dL	12,800 (11,100–14,900)	1960 (1670–2310)	6.54 (5.89–7.27)
CL, mL/h/kg	0.51 (0.44–0.59)	3.31 (2.81–3.88)	0.15 (0.14–0.17)
IR, IU/dL per IU/kg	2.48 (2.18–2.82)	2.11 (1.79–2.49)	1.18 (1.10–1.26)

Efanesoctocog alfa mean (range) FVIII activity post-infusion was 51% (35-72%) at 4 days and 17% (13-23%) at 7 days

Slide Courtesy of Sobi

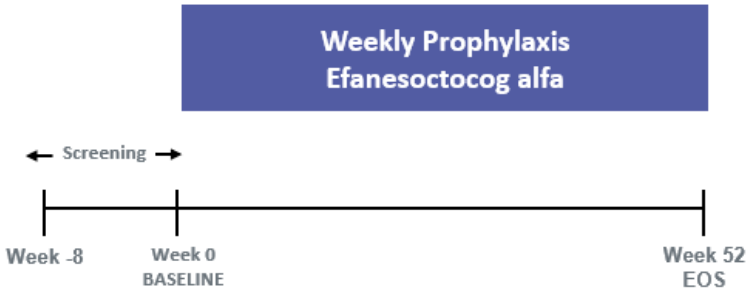
Efanesoctocog alfa
XTEND-Kids

XTEND-Kids: Study Design[1]

A **Phase 3** open-label, multicenter study of the safety, efficacy, and PK of efanesoctocog alfa in previously treated pediatric (< 12 years of age) patients with severe hemophilia A weighing ≥ 10 kg

Estimated enrollment: 65 previously treated patients[a]

- **6 to < 12 years:** previous treatment for ≥ 150 EDs
- **< 6 years:** previous treatment for > 50 EDs



Slide Courtesy of Sobi

Efanesoctocog alfa
XTEND-Kids

Primary endpoint

- Occurrence of inhibitor development

Secondary endpoints

- Annualized bleeding rates (ABRs)
- Efanesoctocog alfa consumption
- Joint health outcomes (HJHS, target joint resolution)
- Quality of Life (Haemo-QoL)
- Treatment of bleeds
- Perioperative management
- Safety and Tolerability
- PK

HJHS, Hemophilia Joint Health Score; Haemo-QoL, Hemophilia quality of life questionnaire for children.
PK, pharmacokinetics
1. ClinicalTrials.gov NCT04759131 Efanesoctocog alfa is currently under clinical investigation, and its safety and efficacy have not been evaluated by any regulatory authority

Slide Courtesy of Sobi

UKS