Therapeutische Antikörper in der Hämostaseologie

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Erklärungen

Der Vortragende hat Honorare für Beratertätigkeiten und Vorträge sowie Forschungs- und Reisekostenunterstützungen von Ablynx/Sanofi, Alexion, Biotest, CSL-Behring, Novo Nordisk, Roche, Takeda und Technoclone erhalten.

Er ist Mitglied der Steuerungsgruppen von mehreren klinischen Studien.

Alle Begriffe in diesem Vortrag sind als geschlechtsneutral zu verstehen.

Statements ohne Referenzierung stamen vom ASH Meeting 2022.

Therapeutische Antikörper in der Hämostase

	Antithrombotisch	Prokoagulatorisch	Immunsuppressiv	Komplement-inhibierend
Plasma	Abelacimab (F XI) Osocimab (F XI) Xisomab (F XI) 3F7 (F XII)	Emicizumab (F VIII mimet.) Concizumab (TFPI) Mim8 (F VIII mimet.) VGA039 (Anti-Protein S) SR-Ab8 (mod. Emicizumab)	Efgartigimod (FcRn) Rozanolixizumab (FcRn)	Eculizumab (C5) Ravulizumab (C5)
Thrombozyten	Caplacizumab (VWF) Abciximab (GP IIb/IIIa) ACT017 (GP VI)			
Antidot		Idarucizumab (Dabigatran)		
Sonstiges			Rituximab (CD20)	

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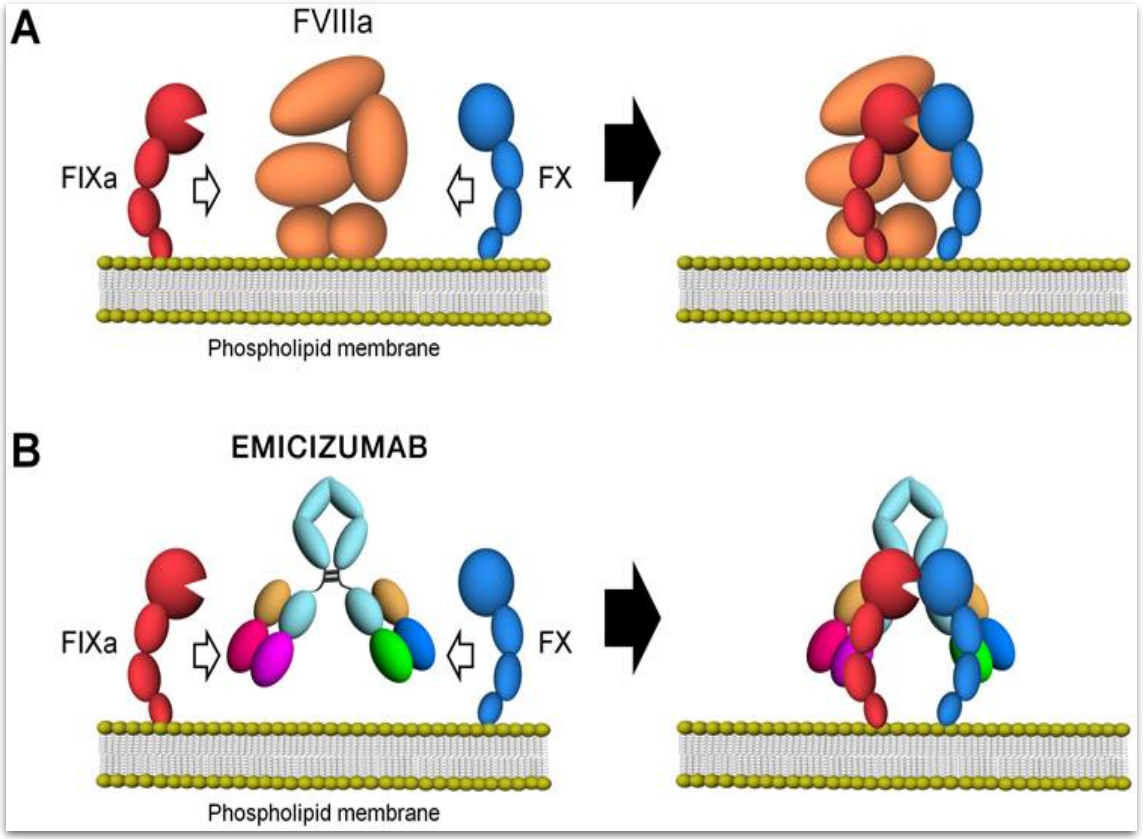
Sonstiges			Rituximab (CD20)	

Emicizumab (Hemlibra®)

- Bispezifischer, Faktor VIII-mimetischer humanisierter therapeutisher Antikörper[1]
- Von FDA und EMA zugelassen zur Behandlung von Pat. mit (kongenitaler) Hämophilie A mit und ohne Inhibitoren
- Hoch effektiv in der Prävention von Spontanblutungen[2]
- Therapieschema: subkutane Injektionen in 1-4 wächigen Intervallen[2]
- Lange Plasma-Halbwertszeit (646 Stunden = 4 Wochen)



(1) Lenting et al.: Blood. 2017;130:2463–8. (2) Oldenburg et al.: N Engl J Med. 2017;377:809–18.

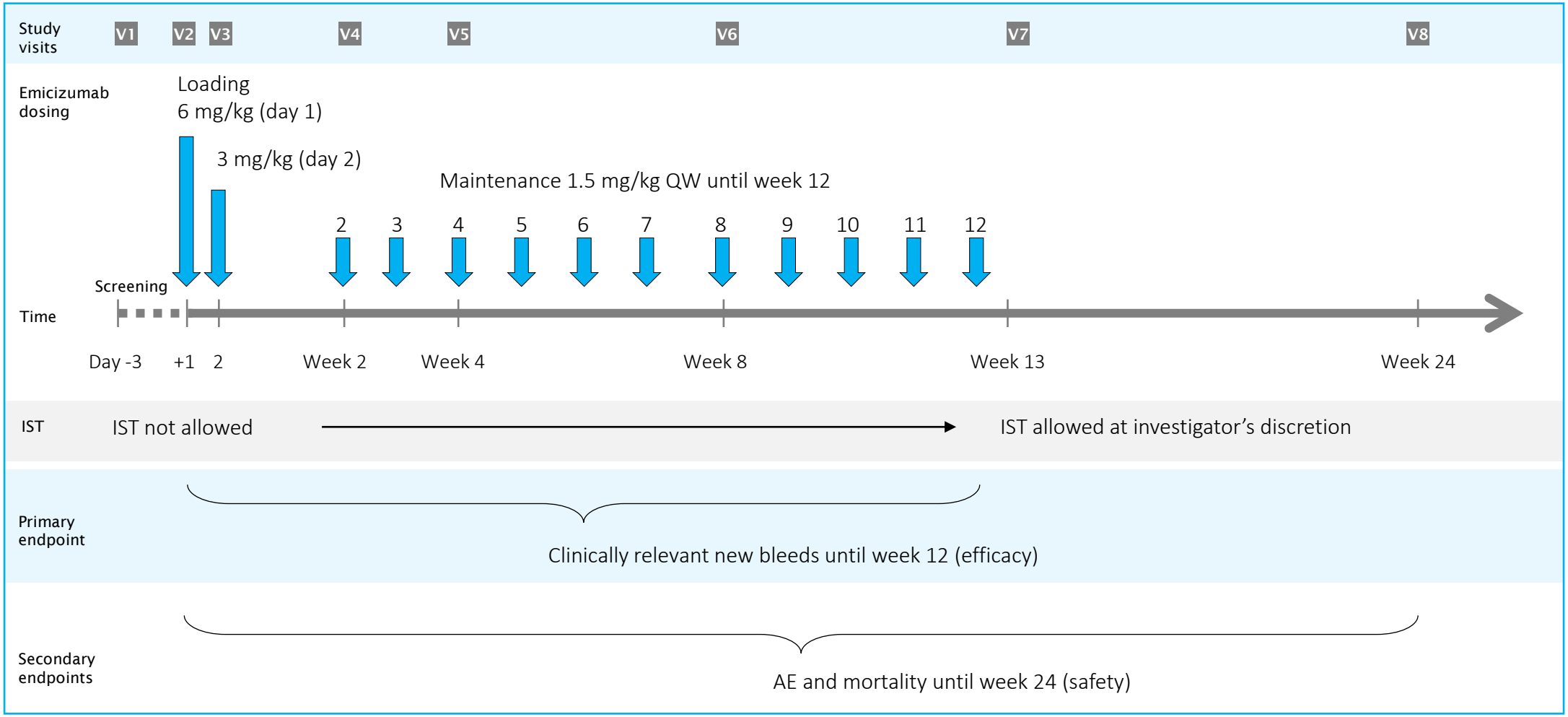
Klinische Vorteile von Emicizumab

- keine häufigen iv. Injektionen mehr notwendig
- alle 2-4 Wochen sc. Gaben
- auch wirksam bei FVIII Hemmstoffen
- keine Stigmatisierung von Kleinkindern
- weniger Hemmstoffentwicklung, da weniger Kontakt mit FVIII ???
- auch kleinere Operationen sind unter Emicizumab möglich

Emicizumab auch bei erworbener (autoimmun) Hämophilie A vorteilhaft

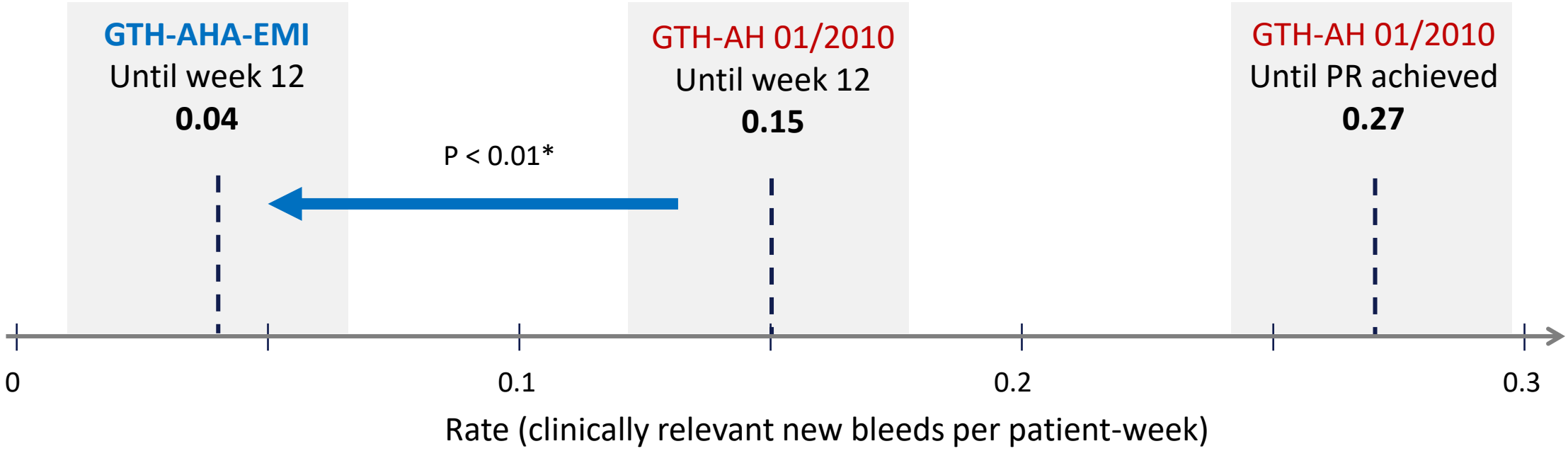
- **Wiener Daten:**
  - Knoebl et al. Emicizumab for the treatment of acquired hemophilia A. Blood. 2021 Jan 21;137(3):410-419. doi: 10.1182/blood.2020006315: **Erste umfassende Publikation von 12 Patientinnen**
  - Knoebl et al: Emicizumab for the treatment of acquired hemophilia A: an update of the Vienna experience. ISTH 2022: **Auswertung von 25 Patient/innen**
- **GTH AHA-EMI Studie (prospektiv, offen, multizentrisch):**
  - 47 Patient/innen, hochsignifikante Reduktion von Blutungen und Mortalität: Lancet Haematology 2023, in press.
- **Japanische Daten:**
  - Shima et al, A prospective, multicenter, open-label phase III study of emicizumab prophylaxis in patients with acquired hemophilia A, Journal of Thrombosis and Haemostasis, 2022, doi.org/10.1016/j.jtha.2022.10.004 **Zulassungserweiterung in Japan für erw. Hämophilie**

GTH-AHA-EMI study outline



Tiede, Hart, Knöbl et al: Emicizumab prophylaxis in patients with acquired hemophilia A (AHA). Lancet Haematology 2023, in press. NCT04188639

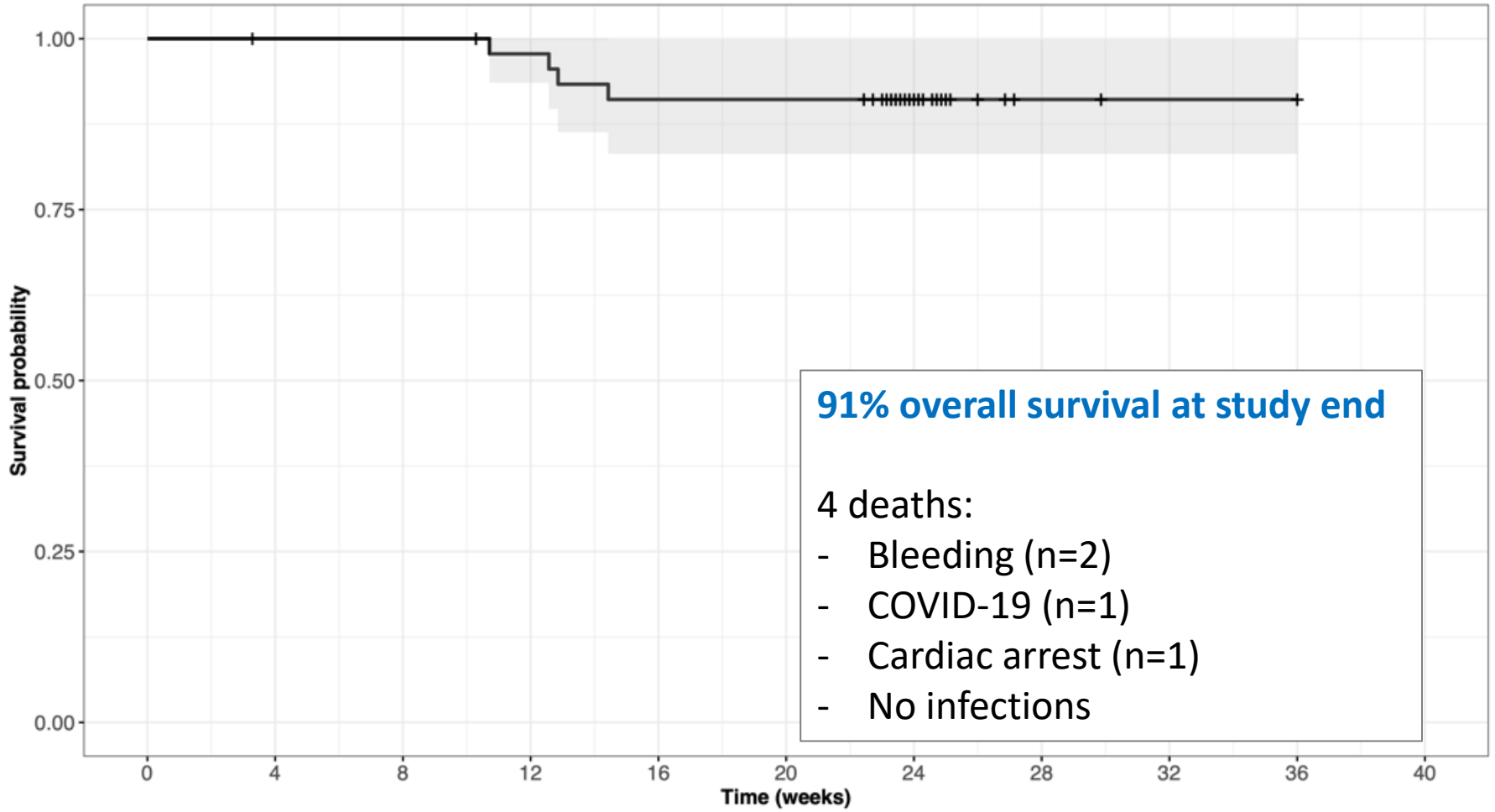
Observed bleeding rate:



* exponential likelihood ratio test (one sample method)

Tiede, Hart, Knöbl et al: Emicizumab prophylaxis in patients with acquired hemophilia A (AHA). Lancet Haematology 2023, in press. NCT04188639

Overall survival

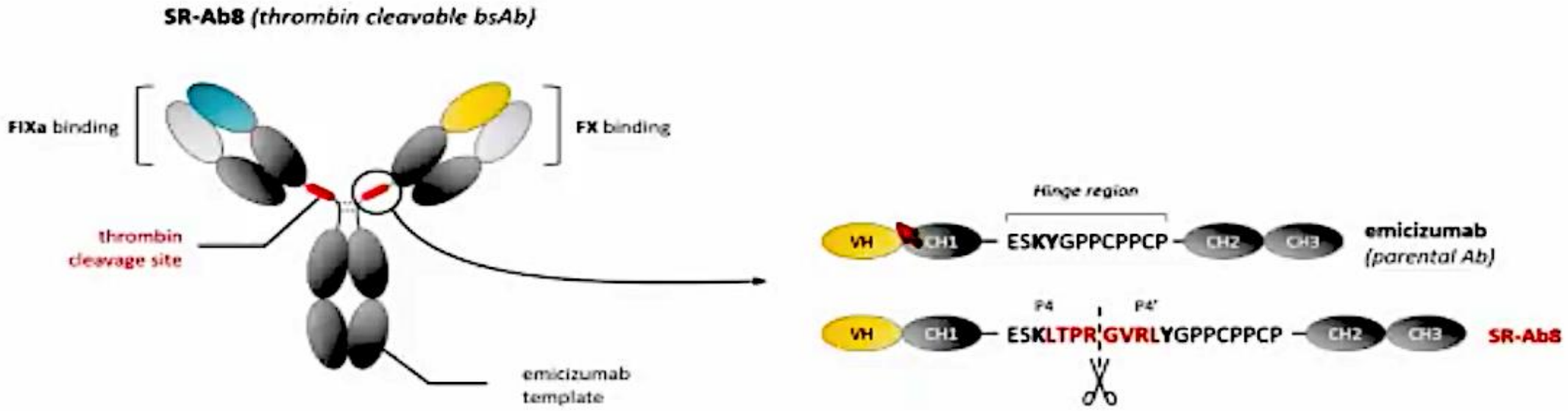


Tiede, Hart, Knöbl et al: Emicizumab prophylaxis in patients with acquired hemophilia A (AHA). Lancet Haematology 2023, in press. NCT04188639

Emicizumab Variante: SR-Ab8:

Muczynski et al: A FVIII-Mimetic Bispecific Antibody with an Embedded Self-Regulation Mechanism Reduces the Risk of Prothrombotic Events for the Treatment of Haemophilia A

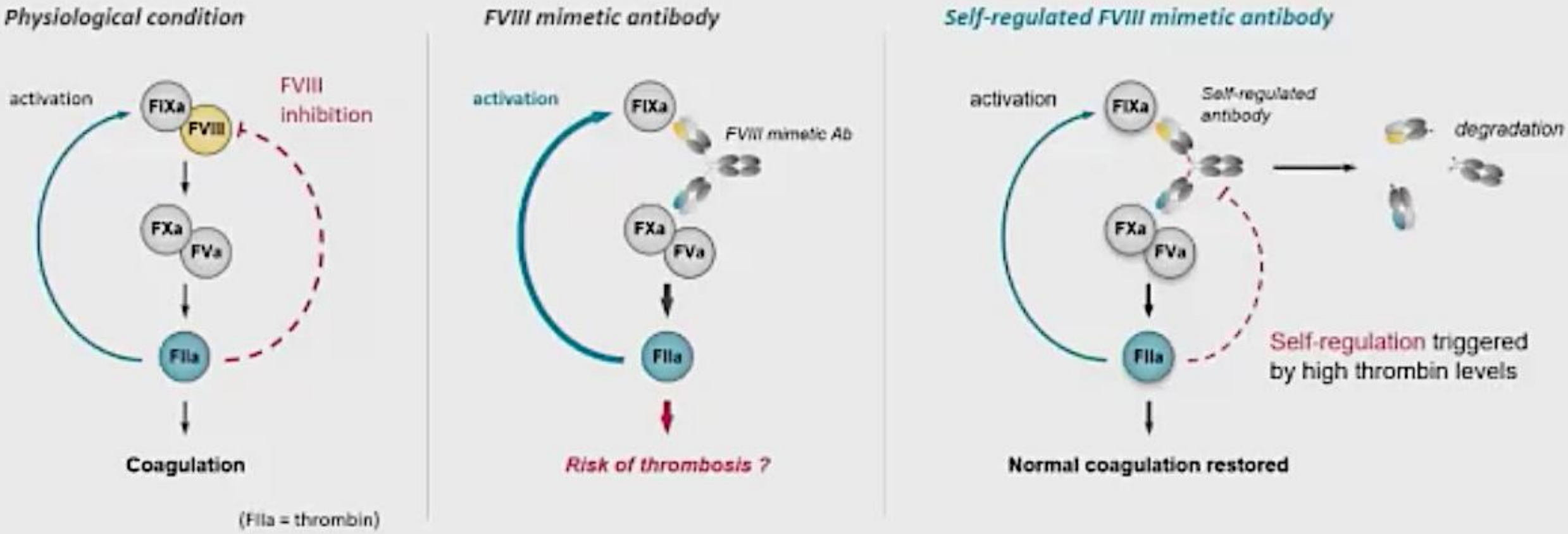
SR-Ab8 : a prototype of self-regulated antibody



- Prototype designed using the backbone of emicizumab
- Several thrombin cleavable peptides were tested before selecting the **LTPRGVRL** synthetic sequence
- The peptide is inserted in the hinge region to achieve deficient inactivation of the antibody

Self-regulation to control the coagulation cascade

⇒ **Thrombin mediated self-regulation** will restore the coagulation balance and reduce the risk of thrombosis

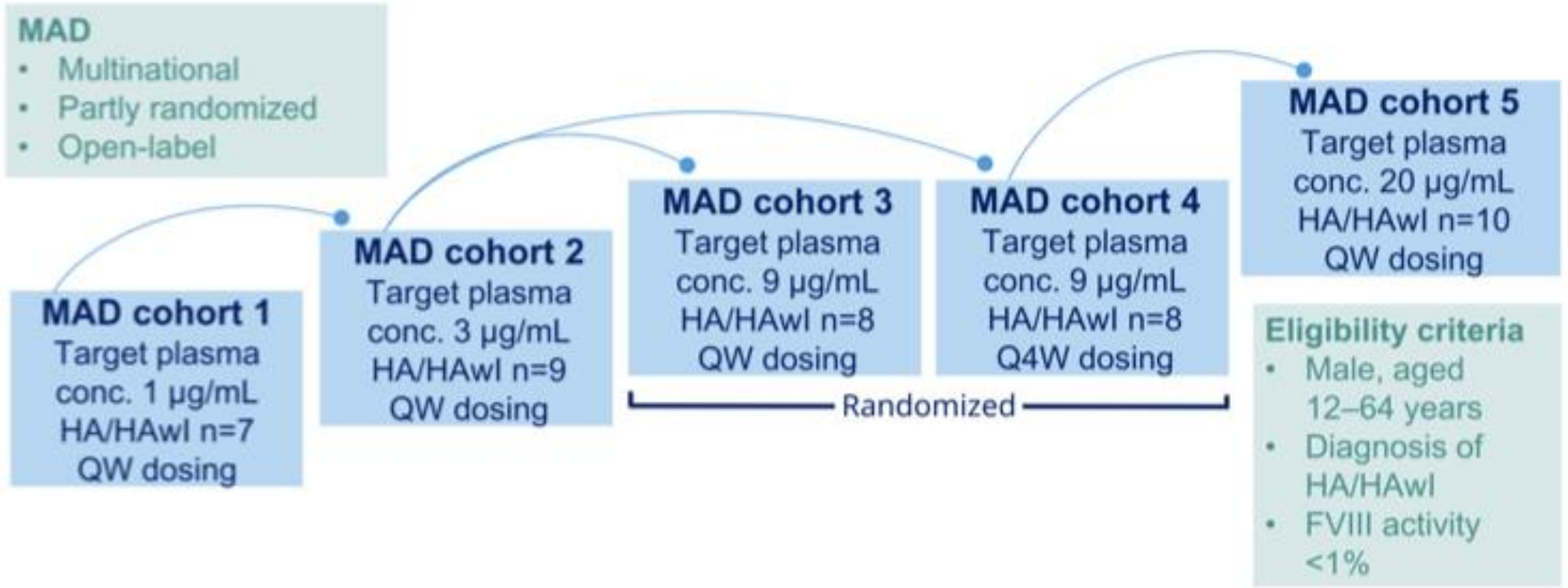


Neuer FVIII-mimetischer Antikörper: **Mim8**

- Next-Generation FVIII Mimetikum, wird zur Zeit in klinischen Studien in Hämophilen mit und ohne Inhibitoren getestet (Novo Nordisk)
- FRONTIER1 (EudraCT: 2019-000465-20): Phase 1/2
- Phase 1 (Sicherheitsprüfung einer Einzeldosis in gesunden Probanden) ist abgeschlossen, keine Sicherheitsbedenken
- Phase 2 (multiple aszendierende Dosierung) ist abgeschlossen

Mim8: Phase 1/2 Studie (FRONTIER 1)

Figure 1. Study design



Mim8: Phase 1/2 Studie (FRONTIER 1)

Figure 2. Mean profiles of Mim8 concentration (linear scale)

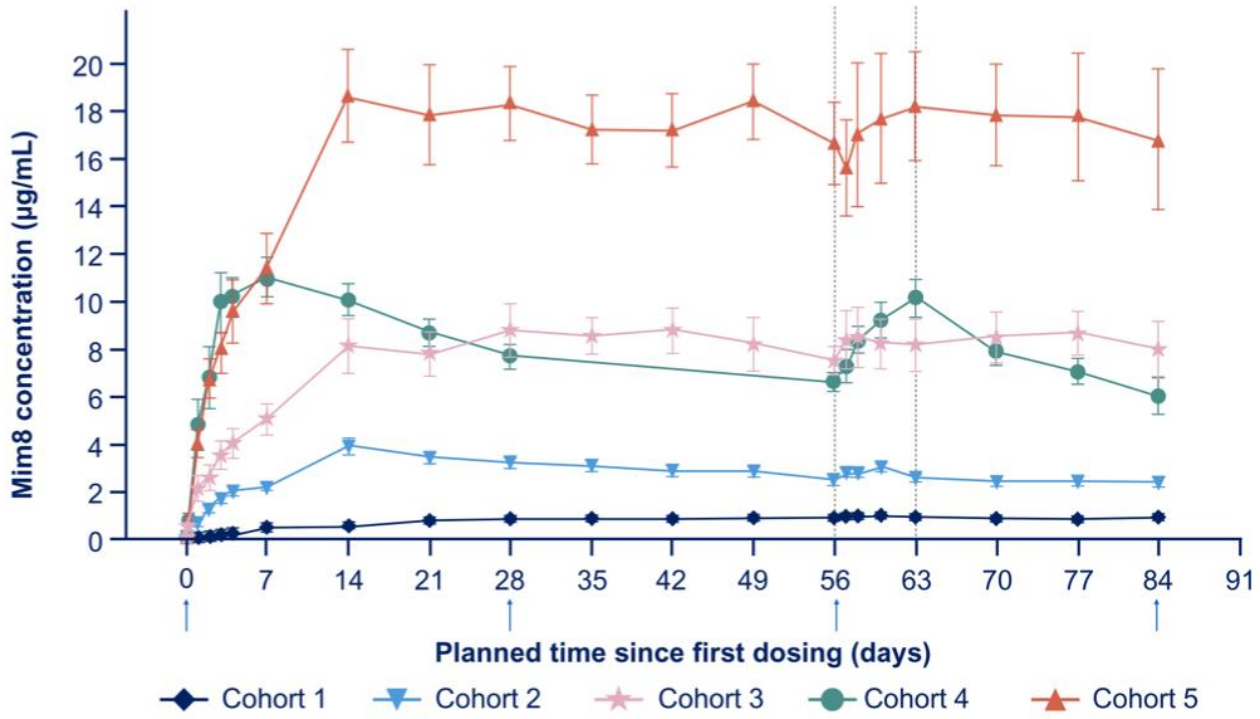
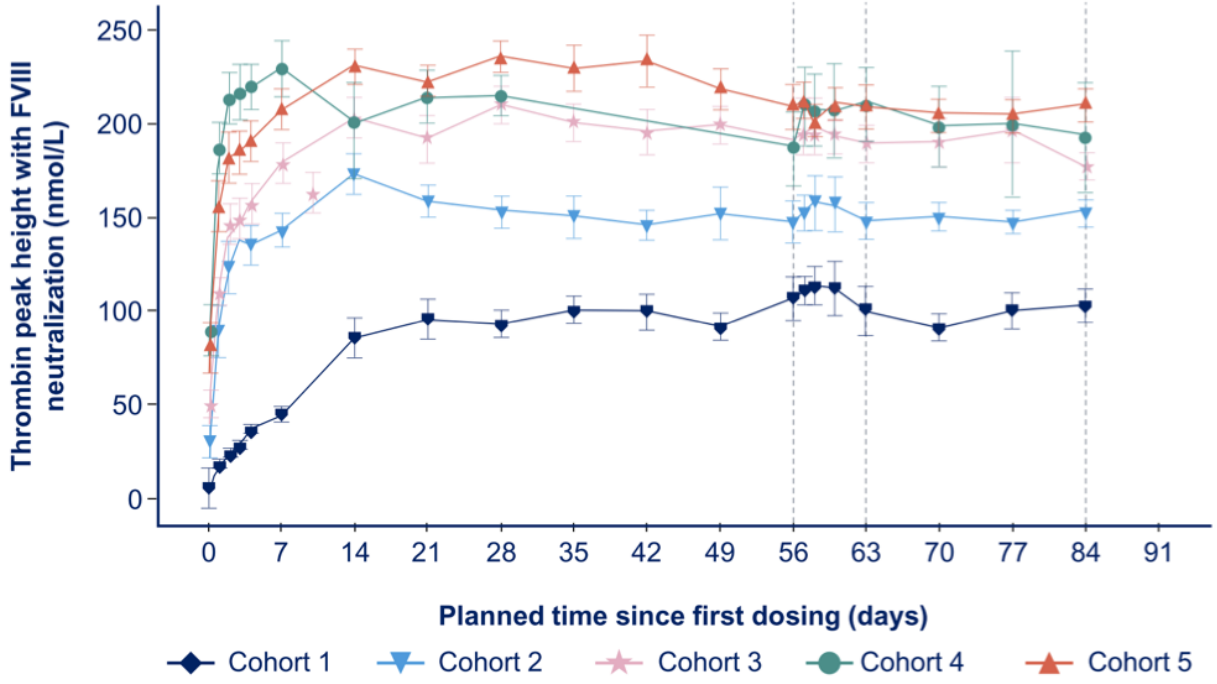


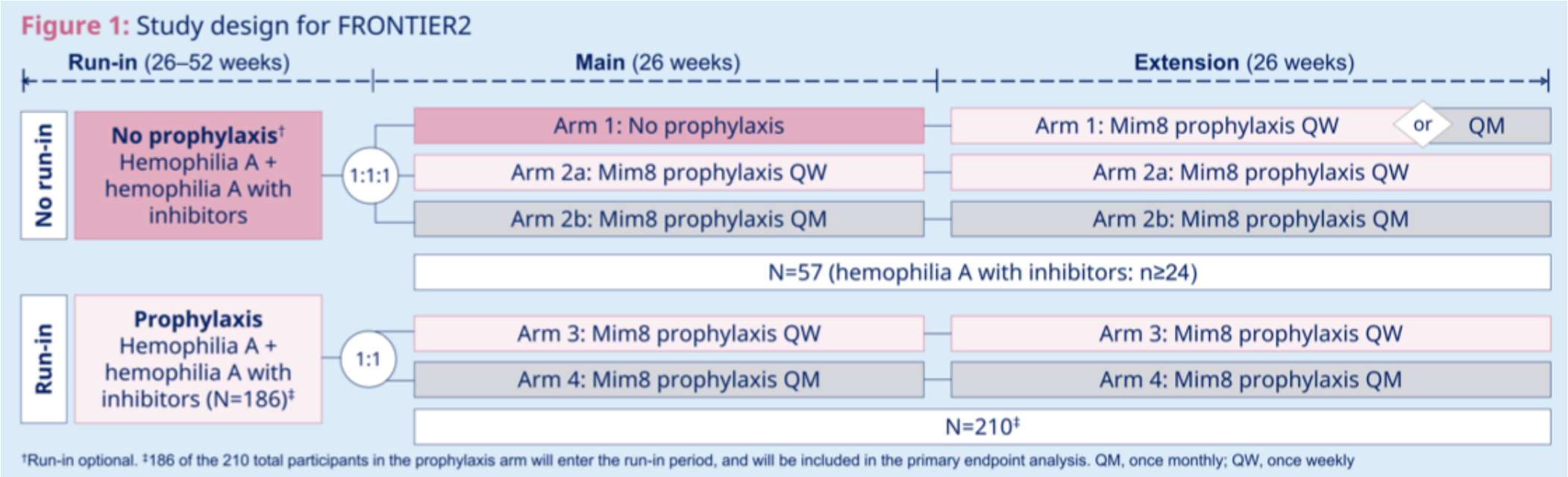
Figure 3. Mean profiles of thrombin peak height (linear scale)

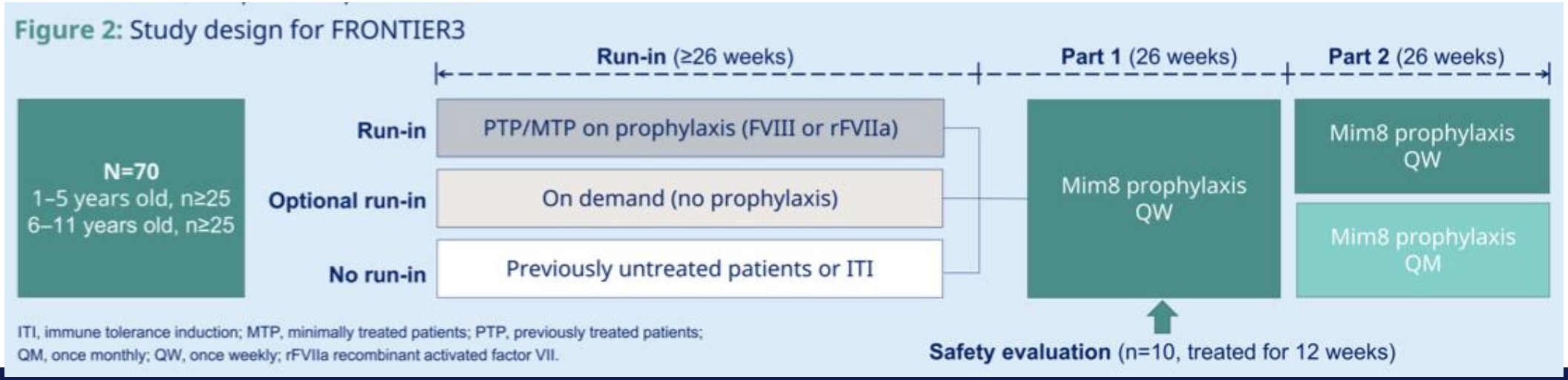


Mim8: Phase 1/2 Studie (FRONTIER 1)

- Akzeptable Sicherheits-Daten:
- Gute Tolerierbarkeit, keine AEs in Abhängigkeit von der Dosis
- Lokalreaktionen an den Einstichstellen in <1%
- Keine Anti-Mim8 Antikörper
- Ein SAE (nicht-kardiale Thoraxschmerzen), unrelated
- Eine Hypersensitivitäts-Reaktion
- Dosis-abhängiger Anstieg des Prothrombinfragments 1+2

Mim8: weitere klinische Entwicklung





Concizumab (Alhemo®)

- TFPI-inhibierender Antikörper
- Wirksame Blutungsprophylaxe auch bei Hämophilie B mit und ohne Inhibitoren
- Tägliche subkutane Injektionen mit Pen
- Zugelassen in Kanada und Australien, Verfahren bei FDA und EMA laufen

TFPI-Inhibierung als hämostatische Therapie bei Hämophilie A und B: **Concizumab (Alhemo®, Novo Nordisk)**

tägl. sc. Injektion mit Pen:

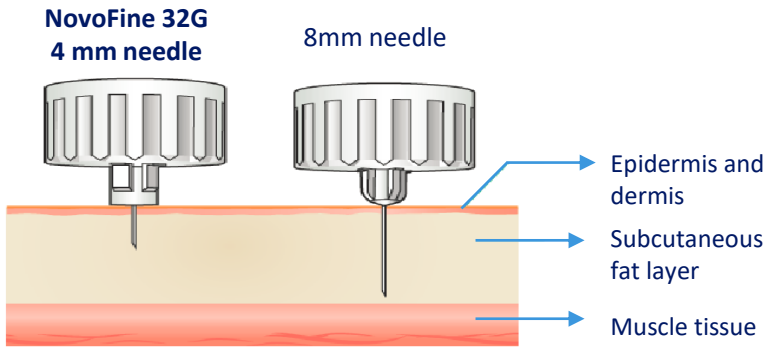
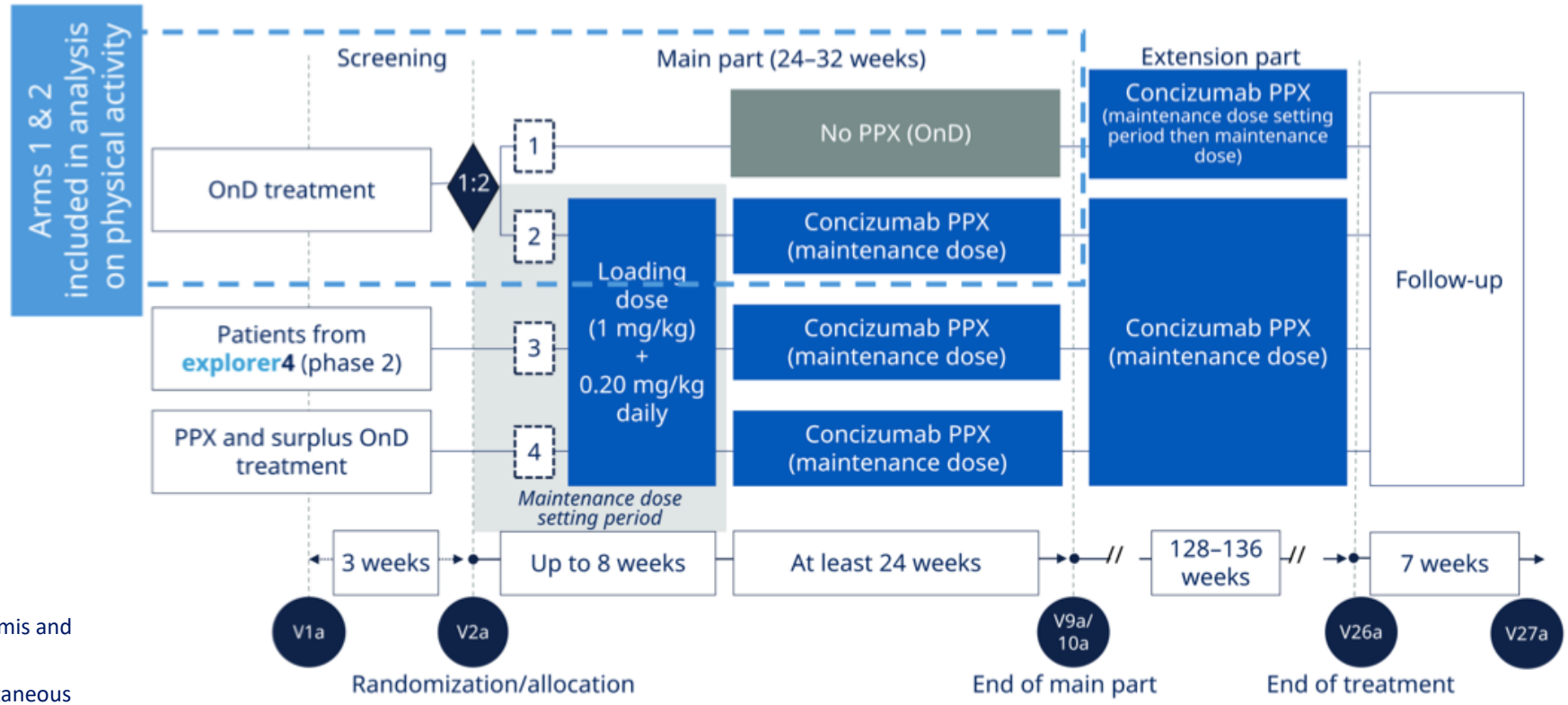
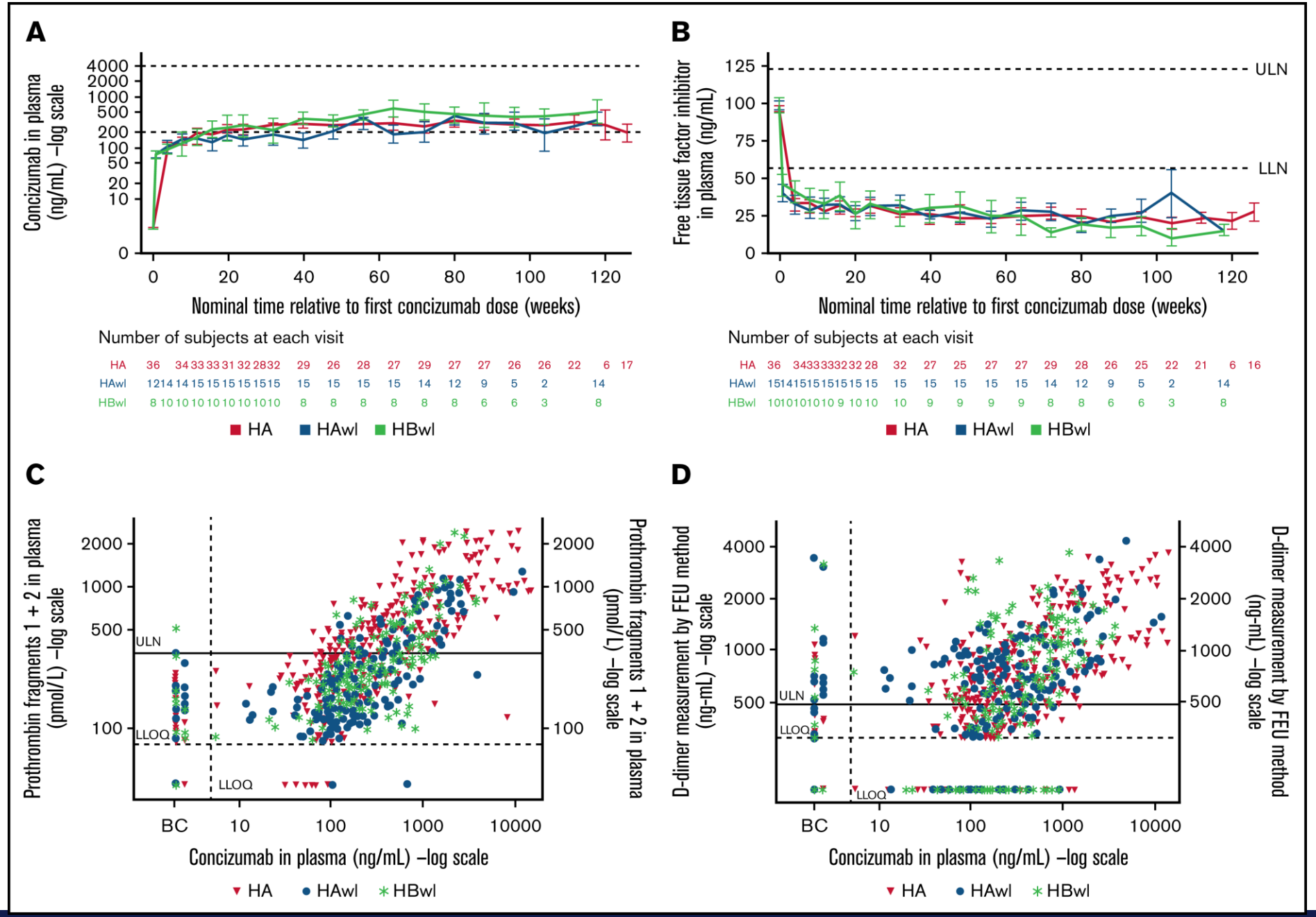


Figure 1. explorer7 trial design





Antikoagulantien:

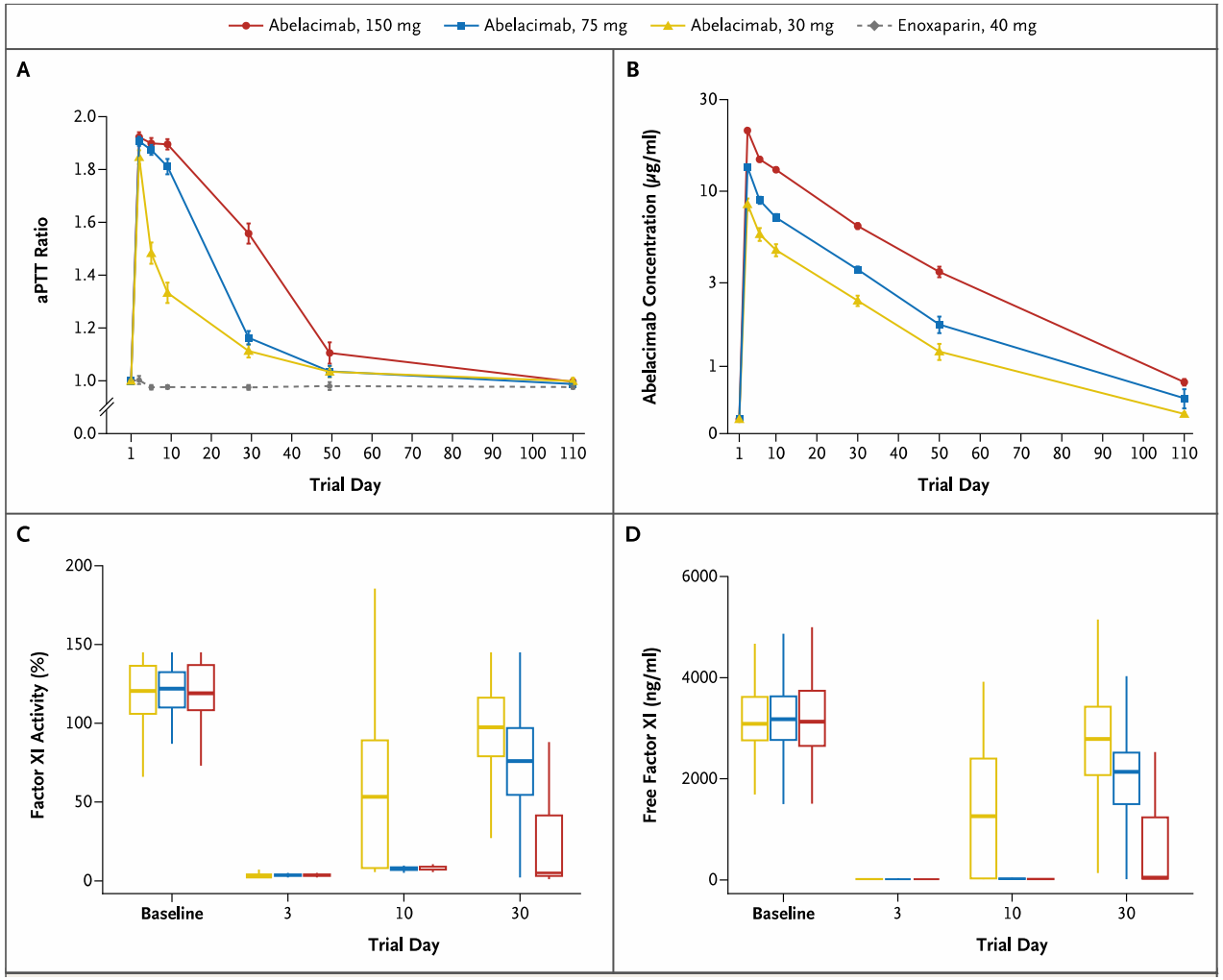
- **FXI Inhibitoren:**
  - Abelacimab (F XI)
  - Osocimab (F XI)
  - Xisomab (F XI)
- Effiziente Antikoagulation mit geringerer Blutungsneigung?

Abelacimab

- Abelacimab (MAA868) ist ein humanisierter monoklonaler Antikörper gegen die katalytische Domäne von F XI und verhindert die Aktivierung von F XI durch F XIIa oder Thrombin
- Eine iv. Gabe von Abelacimab bewirkt eine sofortige Dosis-abhängige Reduktion der F XI Aktivität
- Sehr lange Halbwertszeit

Verhamme P, Yi BA, Segers A, Salter J, Bloomfield D, Büller HR, Raskob GE, Weitz JI; ANT-005 TKA Investigators. Abelacimab for Prevention of Venous Thromboembolism. N Engl J Med. 2021 Aug 12;385(7):609-617. doi: 10.1056/NEJMoa2105872. Epub 2021 Jul 19. PMID: 34297496.

Abelacimab zur Thromboseprophylaxe nach Kniegelenksersatz



Verhamme P, Yi BA, Segers A, Salter J, Bloomfield D, Büller HR, Raskob GE, Weitz JI; ANT-005 TKA Investigators. Abelacimab for Prevention of Venous Thromboembolism. N Engl J Med. 2021 Aug 12;385(7):609-617. doi: 10.1056/NEJMoa2105872. Epub 2021 Jul 19. PMID: 34297496.

Table 2. Efficacy and Safety Outcomes.*

Outcome	Abelacimab, 30 mg	Abelacimab, 75 mg	Abelacimab, 150 mg	Enoxaparin, 40 mg
Efficacy				
No. of patients evaluated	102	99	98	101
Primary efficacy outcome: venous thromboembolism†				
Any event — no. of patients (%)	13 (13)	5 (5)	4 (4)	22 (22)
Risk difference, abelacimab vs. enoxaparin — percentage points (95% CI)	−9.2 (−19.4 to 1.1)	−16.8 (−26.0 to −7.6)	−17.8 (−26.7 to −8.8)	NA
P value for superiority of abelacimab to enoxaparin	0.08	<0.001	<0.001	NA
Components of the primary efficacy outcome — no. (%)				
Symptomatic venous thromboembolism	0	0	0	1 (1)‡
Asymptomatic deep-vein thrombosis	13 (13)	5 (5)	4 (4)	21 (21)
Proximal deep-vein thrombosis	1 (1)	0	0	2 (2)
Distal deep-vein thrombosis	12 (12)	5 (5)	4 (4)	20 (20)‡

Verhamme P, Yi BA, Segers A, Salter J, Bloomfield D, Büller HR, Raskob GE, Weitz JI; ANT-005 TKA Investigators. Abelacimab for Prevention of Venous Thromboembolism. N Engl J Med. 2021 Aug 12;385(7):609-617. doi: 10.1056/NEJMoa2105872. Epub 2021 Jul 19. PMID: 34297496.

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Outcome	Abelacimab, 30 mg	Abelacimab, 75 mg	Abelacimab, 150 mg	Enoxaparin, 40 mg
Safety				
No. of patients evaluated	102	104§	99	104
Major or clinically relevant nonmajor bleeding				
From randomization until venography was completed				
Any event — no. of patients (%)	2 (2)	2 (2)	0	0
Risk difference, abelacimab vs. enoxaparin — percentage points (95% CI)	1.9 (–0.7 to 4.6)	1.9 (–0.7 to 4.5)	0	NA
Major bleeding — no. (%)	0	0	0	0
Clinically relevant nonmajor bleeding — no. (%)	2 (2)	2 (2)	0	0
From randomization through day 30 — no. (%)				
Any event	2 (2)	2 (2)¶	0	0
Major bleeding	0	1 (1)	0	0
Clinically relevant nonmajor bleeding	2 (2)	2 (2)	0	0
Receipt of blood transfusion through day 30 — no. (%)	6 (6)	8 (8)	9 (9)	7 (7)
Adverse events — no. of patients (%)				
Serious adverse event	1 (1)‖	3 (3)	1 (1)	0

Verhamme P, Yi BA, Segers A, Salter J, Bloomfield D, Büller HR, Raskob GE, Weitz JI; ANT-005 TKA Investigators. Abelacimab for Prevention of Venous Thromboembolism. N Engl J Med. 2021 Aug 12;385(7):609-617. doi: 10.1056/NEJMoa2105872. Epub 2021 Jul 19. PMID: 34297496.

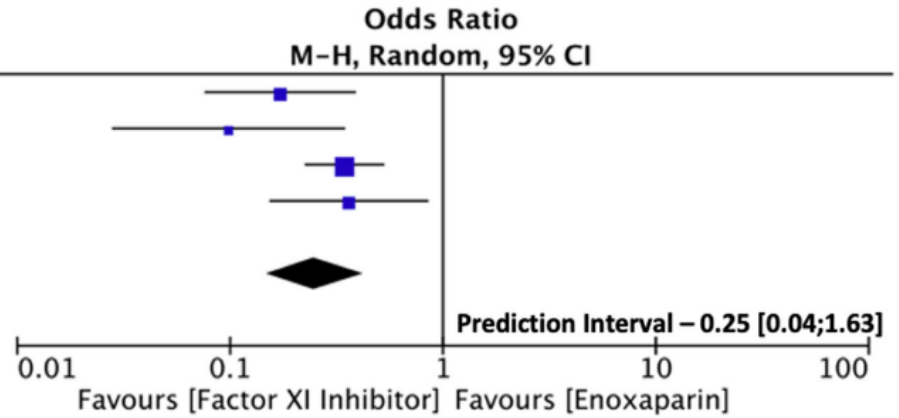
Metaanalyse: Faktor XI Inhibitoren als Antikoagulantien mit geringerer Blutungsneigung?

Effizienz: Verhinderung von Thrombosen:

	Factor XI Inhibitor		Enoxaparin			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Abelacimab ≥75mg	9	197	22	101	23.5%	0.17 [0.08, 0.39]
IONIS-FXIRx 300mg	3	71	22	71	12.9%	0.10 [0.03, 0.35]
Milvexian ≥100mg/day	44	512	54	252	41.4%	0.34 [0.22, 0.53]
Osocimab 1.8mg/kg pre-op	9	80	20	77	22.1%	0.36 [0.15, 0.85]
Total (95% CI)		**860**		**501**	**100.0%**	**0.25 [0.15, 0.42]**
Total events	65		118			

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 5.29$, df = 3 (P = 0.15); $I^2 = 43\%$

Test for overall effect: Z = 5.27 (P < 0.00001)

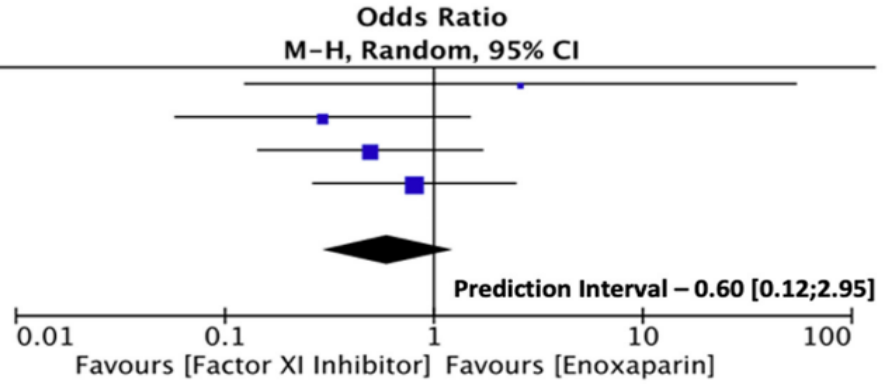


Sicherheit: klinisch relevante schwere Blutungen:

	Factor XI Inhibitor		Enoxaparin			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Abelacimab ≥75mg	2	197	0	101	5.6%	2.60 [0.12, 54.58]
IONIS-FXIRx 300mg	2	77	6	72	19.6%	0.29 [0.06, 1.50]
Milvexian ≥100mg/day	5	592	5	296	33.6%	0.50 [0.14, 1.73]
Osocimab 1.8mg/kg pre-op	6	107	7	102	41.2%	0.81 [0.26, 2.49]
Total (95% CI)		**973**		**571**	**100.0%**	**0.60 [0.29, 1.24]**
Total events	15		18			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.98$, df = 3 (P = 0.58); $I^2 = 0\%$

Test for overall effect: Z = 1.38 (P = 0.17)

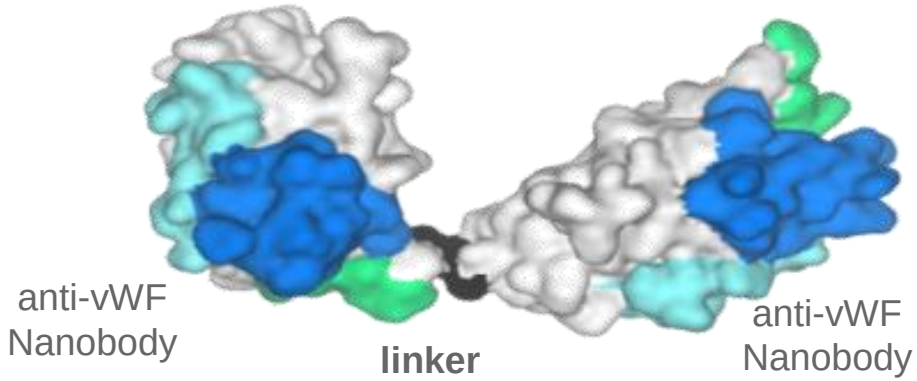


Presume J, Ferreira J, Ribeiras R, Mendes M. Achieving higher efficacy without compromising safety with factor XI inhibitors versus low molecular weight heparin for the prevention of venous thromboembolism in major orthopedic surgery-Systematic review and meta-analysis. J Thromb Haemost. 2022 Dec;20(12):2930-2938. doi: 10.1111/jth.15890. Epub 2022 Oct 5. PMID: 36128769.

Caplacizumab (Cablivi®)

Anti-vWF Nanobody zur Behandlung der Autoimmun-TTP

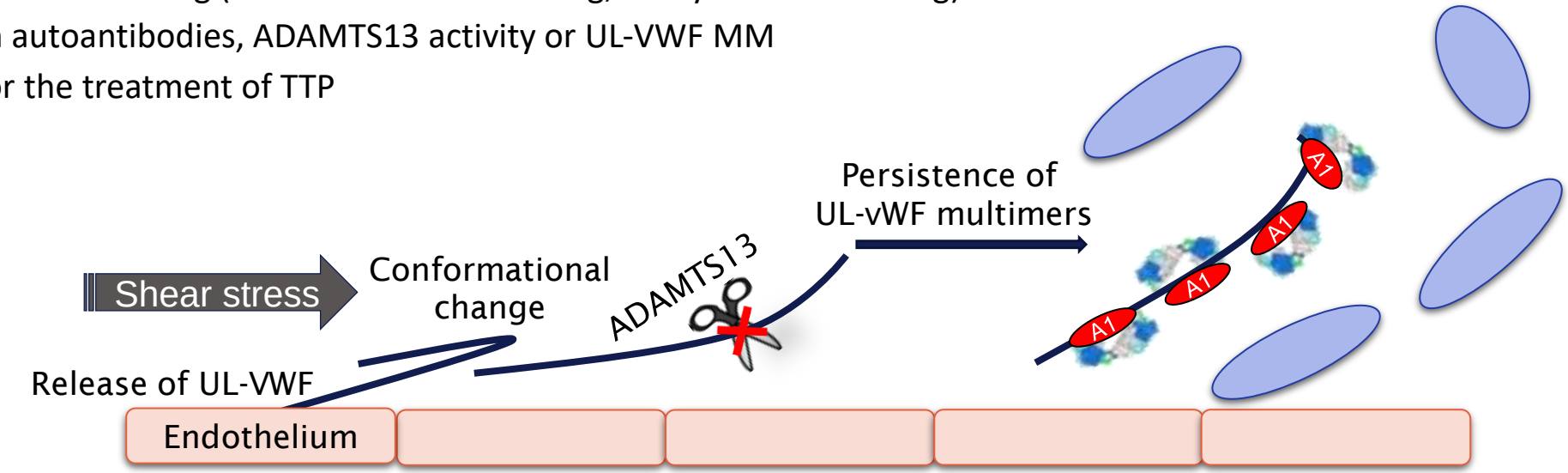
- Highly potent bivalent anti-vWF Nanobody
  - 28 kD bivalent Nanobody
  - selected to bind specifically to the A1 domain of VWF
  - Produced in *E. coli*
  - It competes with the binding of platelets to VWF.



Structure : courtesy of Steyaert et al, VUB

Caplacizumab (Cablivi®)

- 28 kD bivalent nanobody to VWF A1 domains of VWF
- Produced in E. coli recombinant technology
- Competes with the binding of platelets to VWF.
- Immediate effect on platelet string formation and the formation of microthrombi
- Faster increase of platelet counts and improvement of organ function
- Reduction in TTP exacerbations and refractoriness
- Reduction in PEX treatments, PEX volume, ICU days
- Increased risk for bleeding (mucocutaneous bleeding, rarely severe bleeding)
- No effect on autoantibodies, ADAMTS13 activity or UL-VWF MM
- Approved for the treatment of TTP



Peyvandi F, et al. *N Engl J Med. 2016;374(6):511-522.* ***Scully M, et al.*** *N Engl J Med. 2019; 380(4):335-346.* ***Peyvandi F, et al****. Blood. 2021;5(8):2137-2141.*

Most important effects of caplacizumab

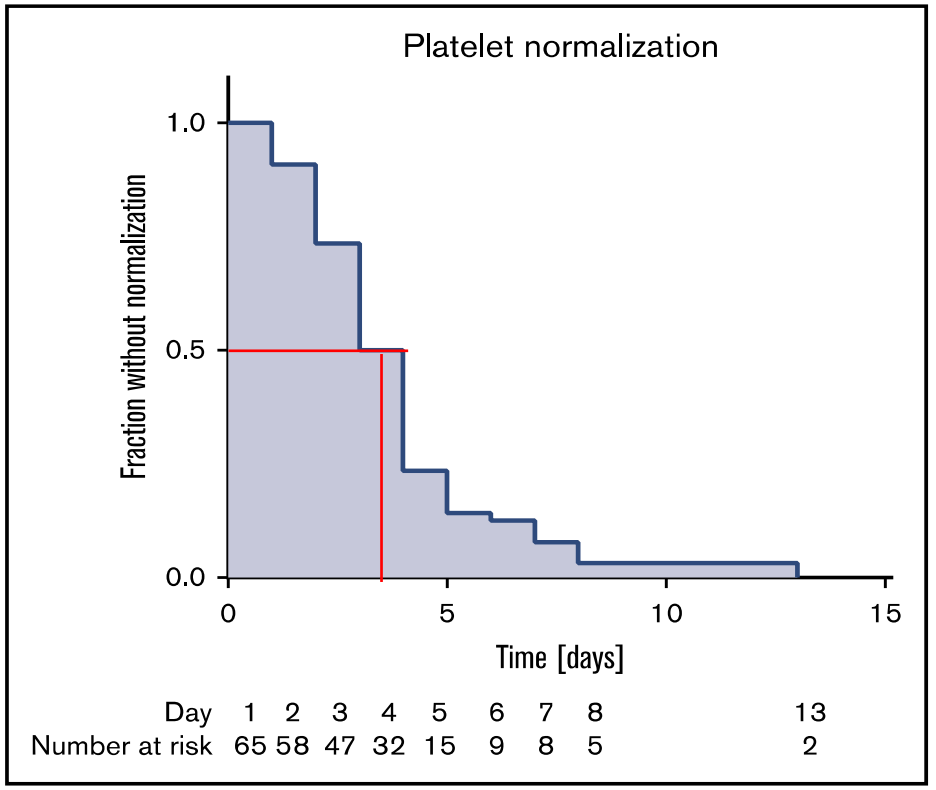
Fast and sustained termination of microangiopathy (with and without additional PEX):

- Immediate PLT increase within hours
- PLT >150 G/L within 3-5 days; almost all within 1 week
- Reduction of organ damage markers

Prevention of exacerbations during and after PEX

- Sustained PLT stabilisation in 96 % of patients
  (vs. 40% exazerbations in controls)

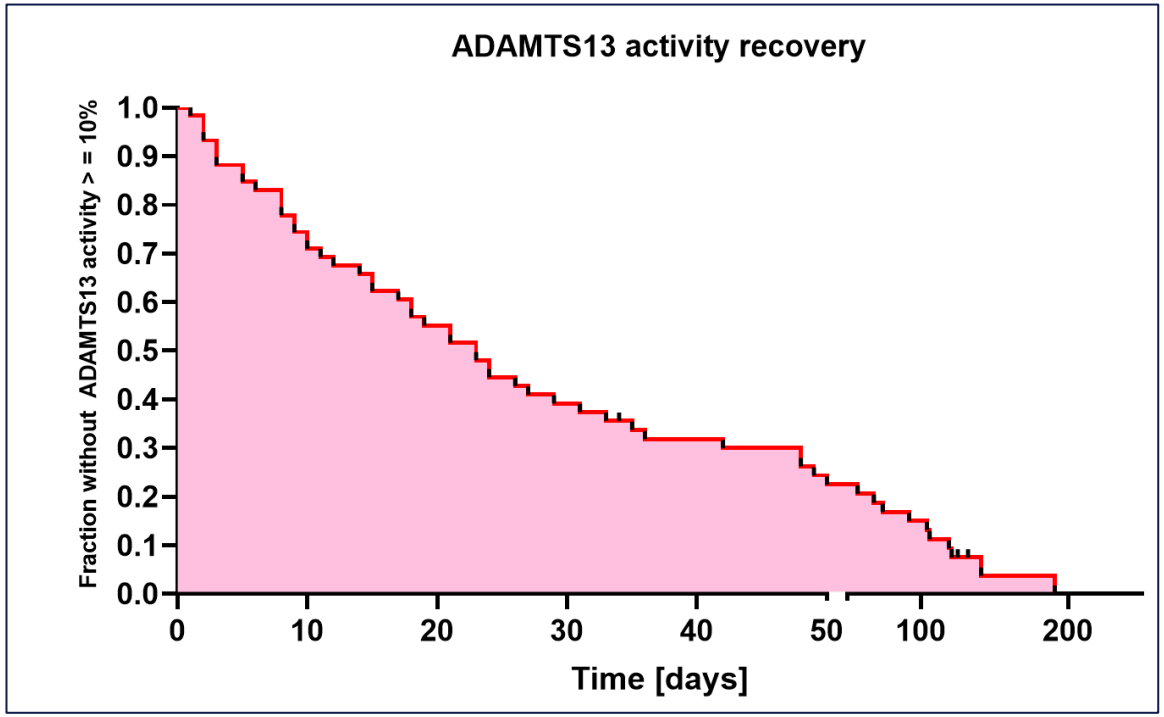
50 % reduction of resource consumption



Völker LA, et al. *Real-world data confirm the effectiveness of caplacizumab in acquired thrombotic thrombocytopenic purpura. Blood Adv. 2020;4(13):3085-3092.*

Notwendigkeit einer effizienten Immunsuppression:

- Auch nach Normalisierung der Thrombozytenzahlen (Median 3 Tage, IQR 1-13 Tage) ist die ADAMTS13 Aktivität meist noch niedrig
- Mediane Zeit bis zur ADAMTS13 Regeneration (>10%) 21 Tage (IQR 1-191) nach Thrombozyten-Normalisierung bzw. 32,5 Tage nach Therapiebeginn (IQR 8-204)



Völker LA, Kaufeld J, Miesbach W, et al. ADAMTS13 and VWF activities guide individualized caplacizumab treatment in patients with aTTP. Blood Adv. 2020;4(13):3093-3101. doi:10.1182/bloodadvances.2020001987

TTP treatment algorithm without PEX

Patient with suspected TTP (severe ADAMTS13 deficiency or high PLASMIC score)

Avoid platelet transfusions
Diagnostic samples and procedures
First injection 10 mg caplacizumab iv. and methylprednisone 100 mg iv.
Monitoring vital signs and neurology
Prepare for PEX (blood group typing; ordering frozen plasma, but not thawing; allocating time/team/machines for PEX)
but no CVL, and do not start PEX

Re-test platelet counts and organ function parameters 4–6 hrs after caplacizumab injection

Improving:
Platelet counts increased, stable organ function →
= response to treatment, PEX no more needed
Continuation of daily 10 mg sc. caplacizumab until ADAMTS13 >10%
Start of rituximab
Daily checks of blood counts and organ function
Organize caplacizumab home therapy
Discharge when PLT >150 G/L

Not improving:
Thawing of frozen plasma, start PEX
Daily evaluation
Stop PEX if platelet counts >150 G/L and stable
Continue caplacizumab 10 mg sc. daily until
ADAMTS13 >10%
Start of rituximab

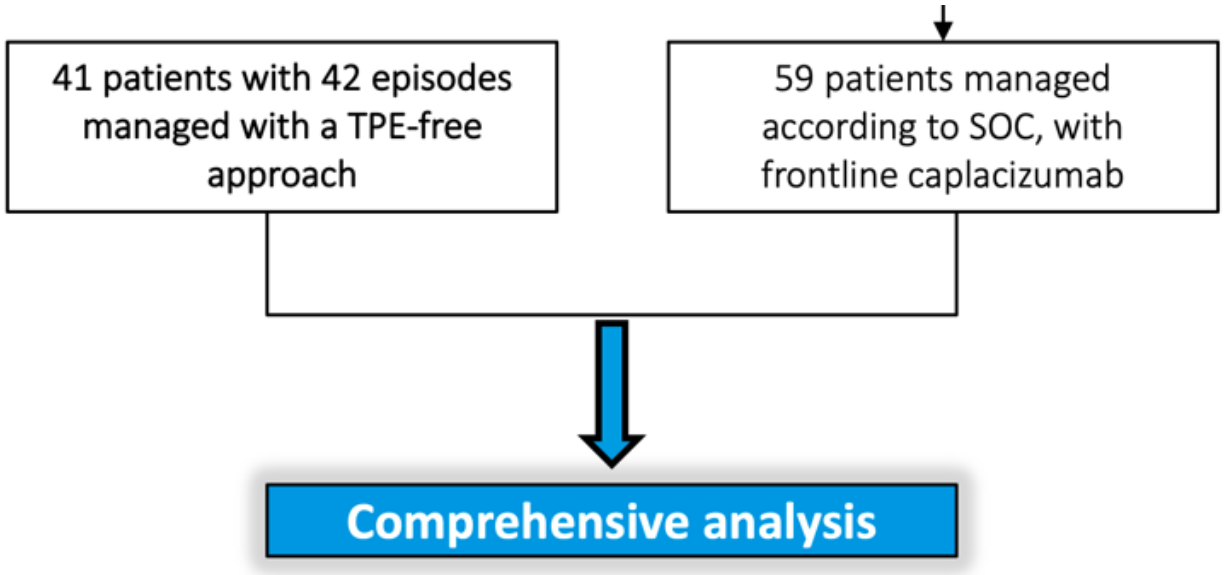
Management of immune thrombotic thrombocytopenic purpura without therapeutic plasma exchange

Germany: REACT-2020 iTTP registry

› 18 patients with 19 iTTP episodes, managed at 9 different medical centers in Germany

Austrian cohort of iTTP patients:

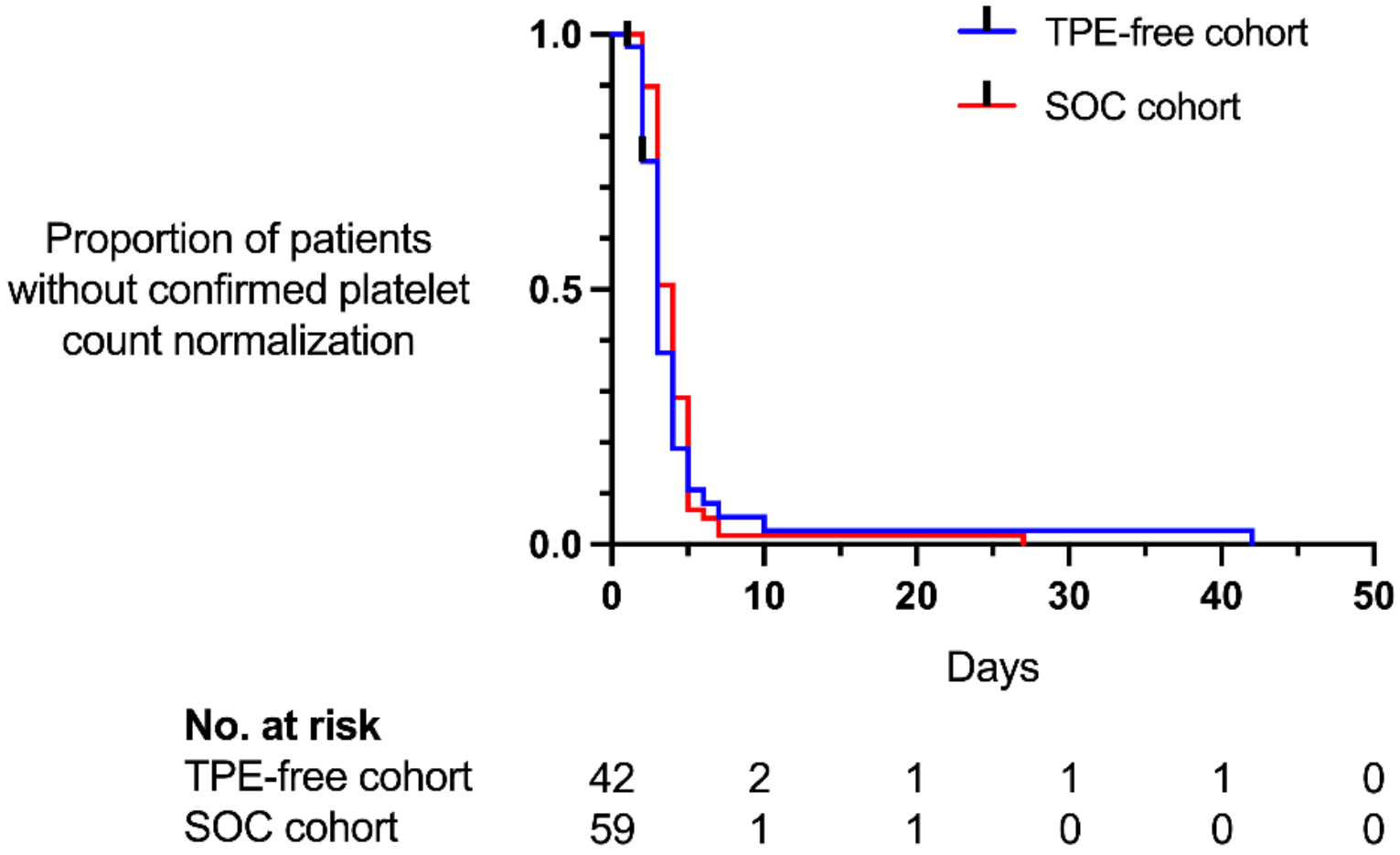
› 23 patients and episodes, managed at 4 different medical centers



Patient characteristics:

Parameter	TPE-free cohort (n = 42)	SOC cohort (n = 59)
Median age (range)	43 (20-83)	47 (20-80)
Female sex (%)	30/41 (73.2)	40 (67.8)
First episode of iTTP (%)	25 (59.5)	38 (64.4)
ADAMTS13 activity < 10% – no. (%)	42 (100)	58 (98.3)
Median platelet count (range), x10E9/l	16 (4-127)	12 (3-52)
Median lactate dehydrogenase (range), U/l	687 (214-2500)	1052 (373-3467)
Elevated troponin – no. (%)	16 (38.1)	27 (45.8)
Median serum creatinine (range), mg/dl	0.96 (0.57-5.3)	1.07 (0.5-3.65)
Glasgow Coma Scale Median (range) Data missing (%)	 15 (13-15) 0 (0)	 15 (3-15) 5 (8.5)
French Severity Score – no. (%) Low (0-1) Intermediate (2) High (3-4) Data missing	 27 (64.3) 10 (23.8) 5 (11.9) 0 (0)	 30 (58.8) 15 (29.4) 6 (11.8) 8 (13.6)

No significant difference in time to platelet count normalization



No. at risk						
TPE-free cohort	42	2	1	1	1	0
SOC cohort	59	1	1	0	0	0

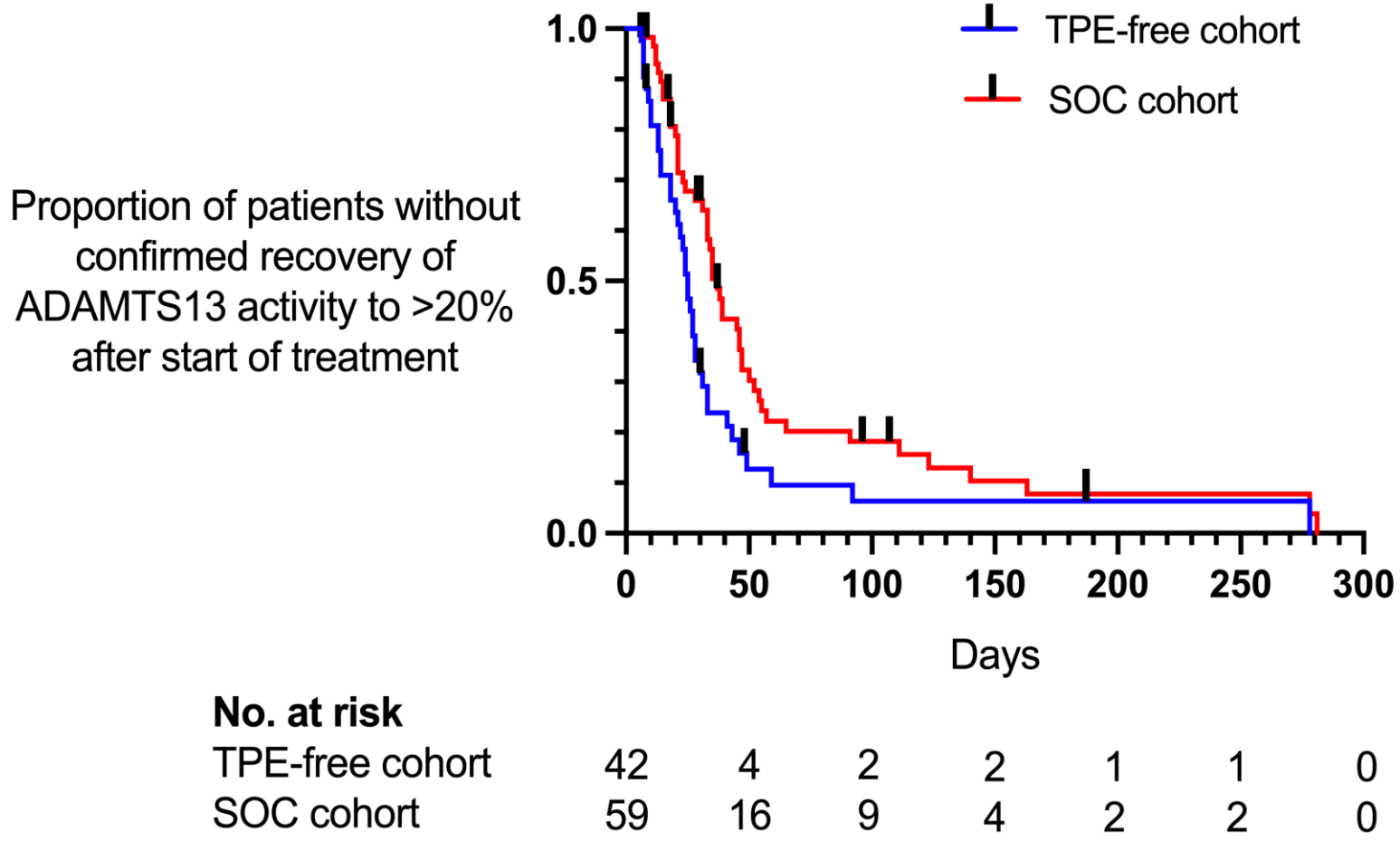
Log rank test

- P value: not significant

Median

- TPE-free cohort: 3 days
- SOC cohort: 4 days

Management without TPE is efficacious in achieving faster ADAMTS13 remission



Log rank test

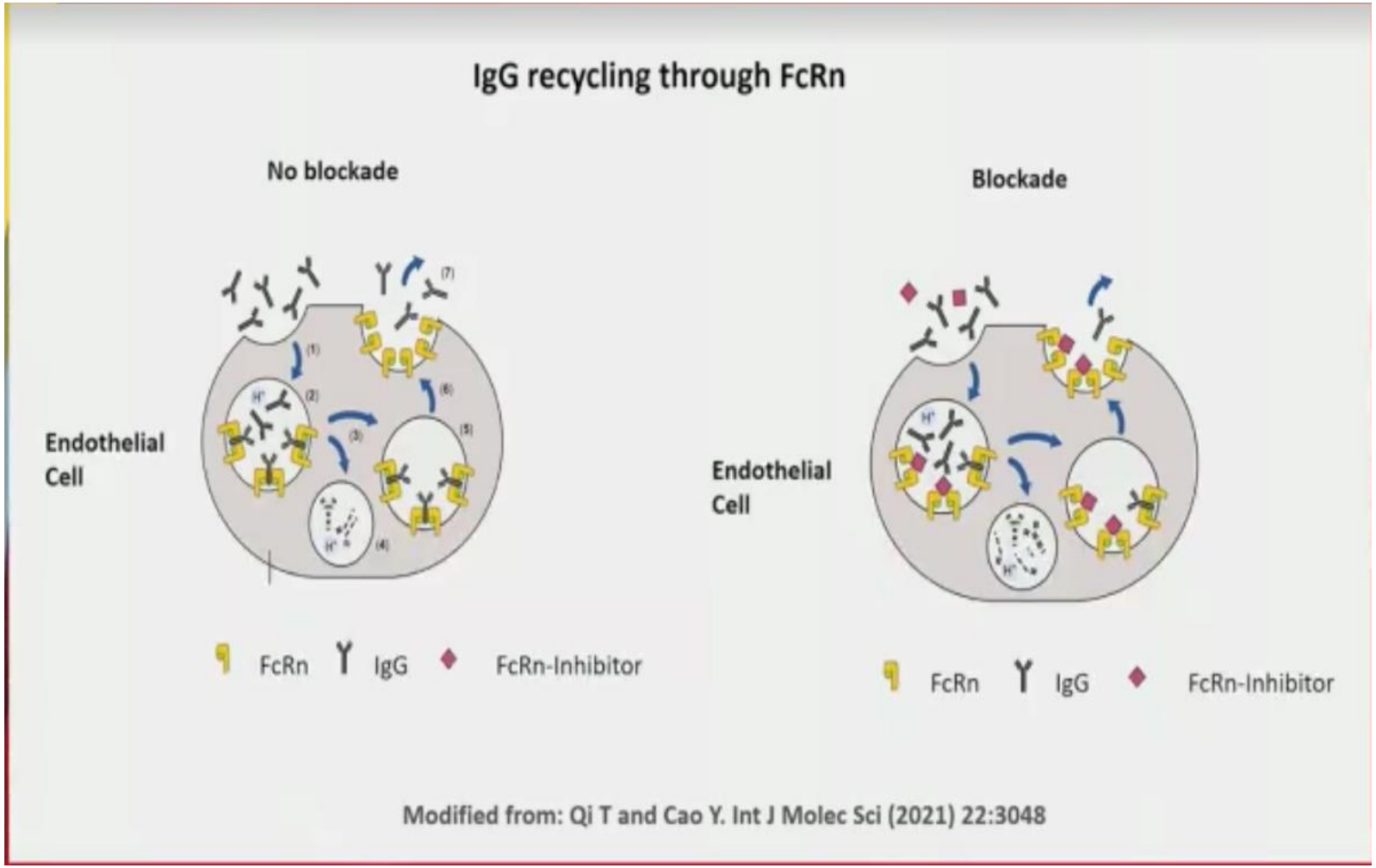
- P value: 0.01

Median

- TPE-free cohort: 25 days
- SOC cohort: 37 days

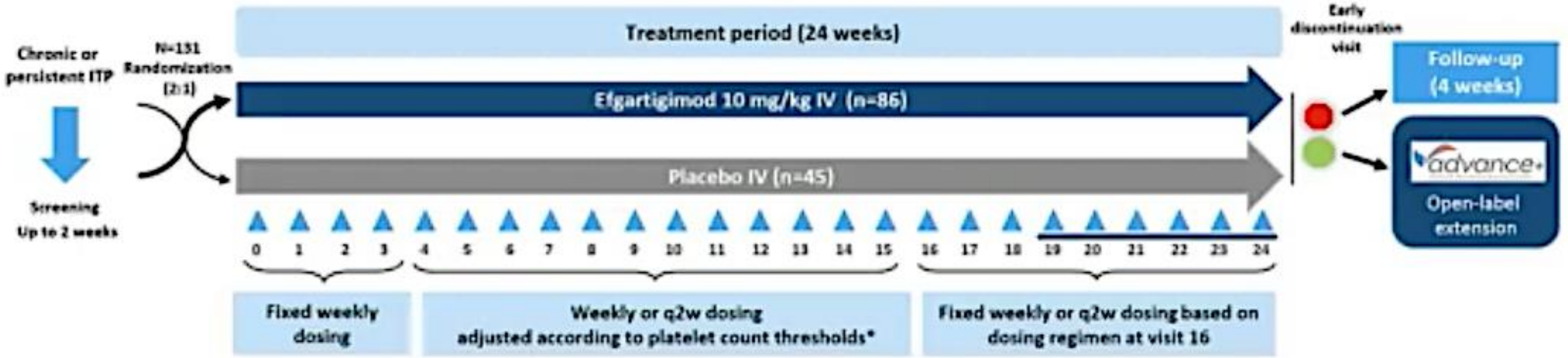
Efgartigimod zur Therapie der Autoimmun-Thrombopenie:

- Efgartigimod alfa ist ein Fragment der Fc-Domäne von humanem IgG1
- Homodimer aus zwei identischen Peptidketten zu jeweils 227 Aminosäuren, über zwei Disulfidbrücken miteinander verbunden
- MG ca. 54 kD
- Rekombinante Produktion in CHO Zellkultur



ADVANCE IV (NCT04188379): Study Design

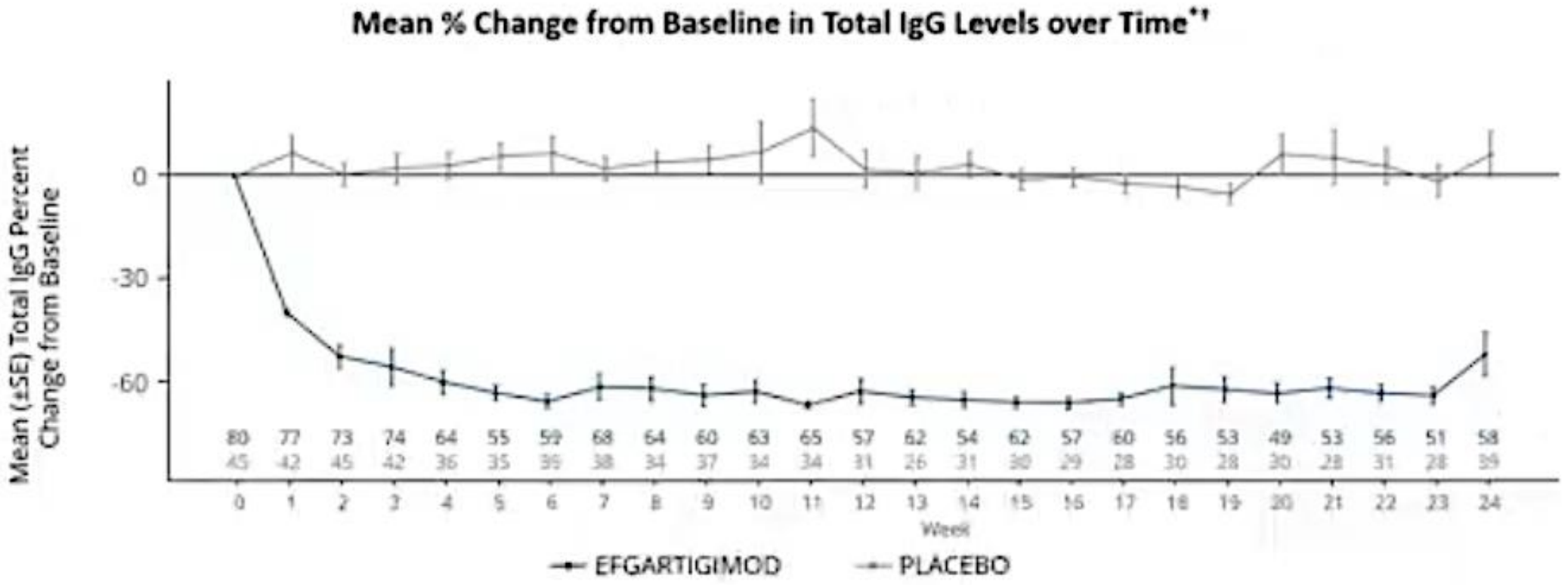
Phase 3, Multicenter, Double-blinded, Placebo-controlled, Randomized Clinical Trial



Eligibility criteria

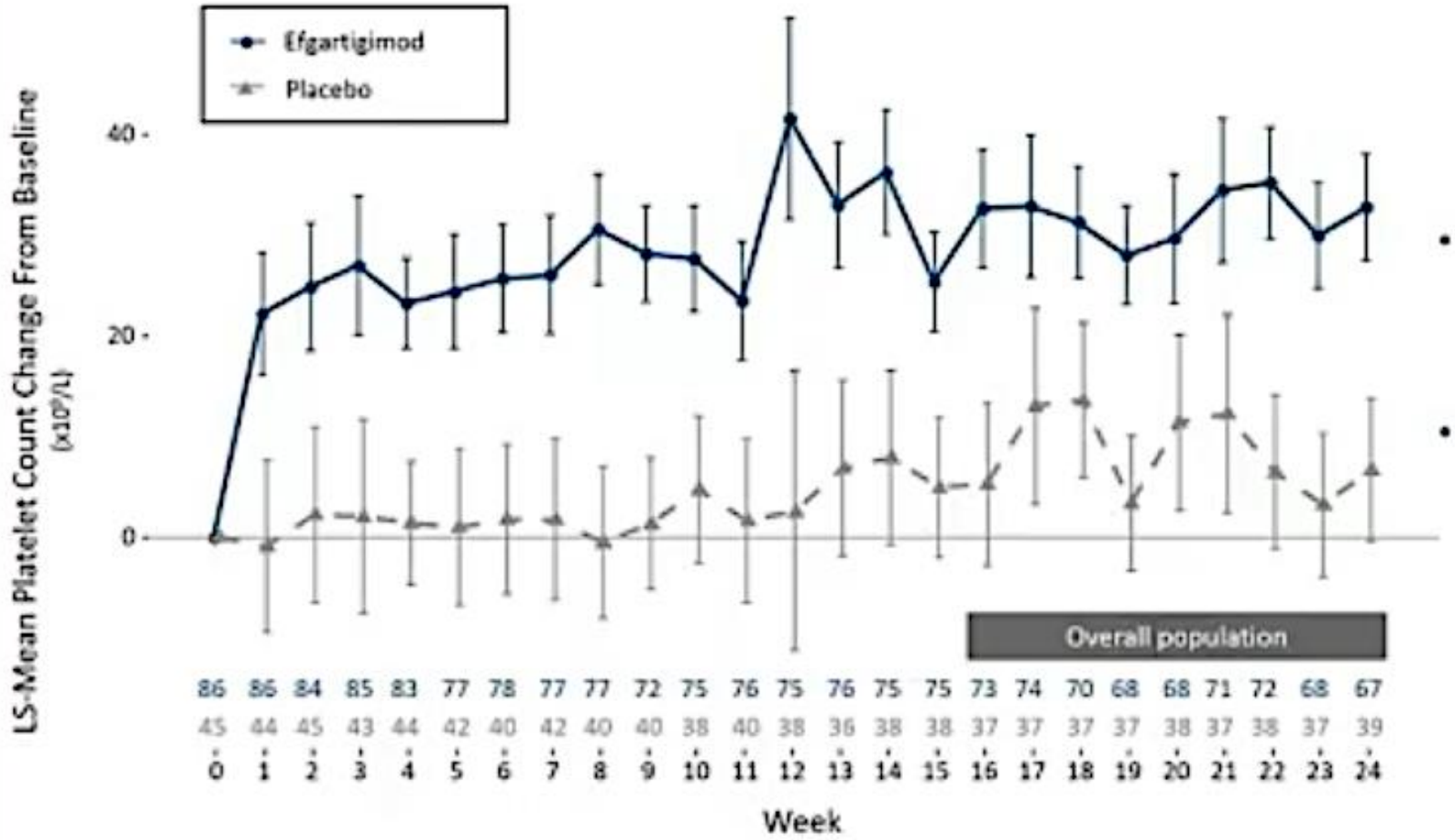
- Age ≥18 years
- Chronic or persistent ITP: Diagnosis supported by a response to a prior ITP therapy
- 2 platelet counts of $<30\times10^9$/L during screening
- At least 2 prior ITP treatments or 1 prior and 1 concurrent treatment
- Concurrent ITP therapy† permitted at stable dose and frequency at study entry and throughout study

Efgartigimod Resulted in Targeted Reduction of IgG Levels*



- Mean IgG levels decreased steadily over the first 4 weeks of treatment, which was sustained across time and corresponded with platelet count responses
  - After the initial decrease in IgG, mean maximum reductions from baseline remained >60% throughout the trial

Efgartigimod Demonstrated Early Sustained Increases in Platelet Counts*



- 33 (38.4%) of efgartigimod treated participants compared to 5 (11.1%) placebo reached a platelet count of $30X10^9$ platelets at week 1
- Sustained platelet count response achieved in 90% (9/10) of participants who switched from weekly to every other week dosing

Zusammenfassung:

- Verschiedene therapeutisch Antikörper für Blutgerinnungsstörungen sind schon verfügbar
- In den letzten Jahren haben einige Präparate Paradigmenwechsel in der Behandlung seltener und komplexer Gerinnungsstörungen bewirkt:
  - Emicizumab bei Hemmstoff-Hämophilie und kongenitaler Hämophilie
  - Caplacizumab bei Autoimmun-TTP
- Weitere Antikörper mit interessanten Wirkmechanismen in Entwicklung