UMC Utrecht
Van Creveldkliniek

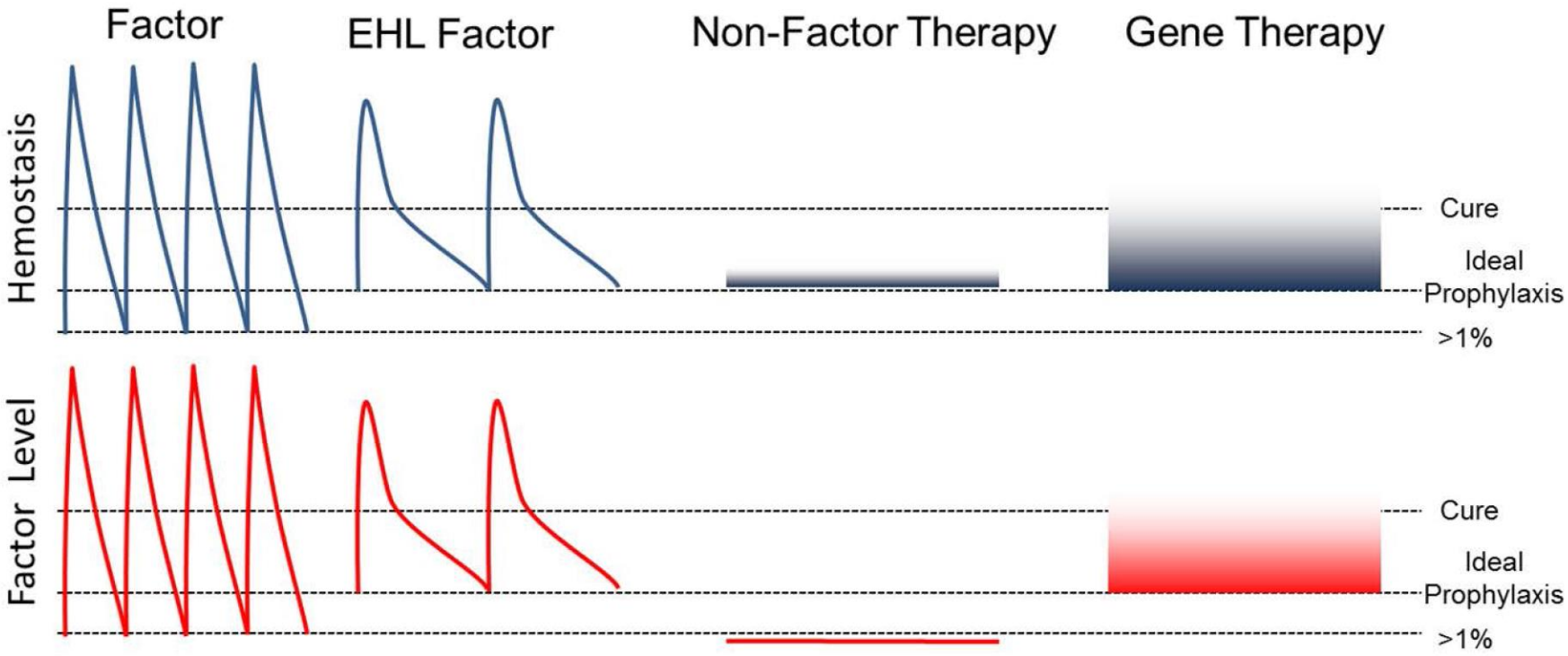
Current use of EHL and non-substitutional therapies

Prof. dr. Roger Schutgens
Van Creveldkliniek
UMC Utrecht

AZU

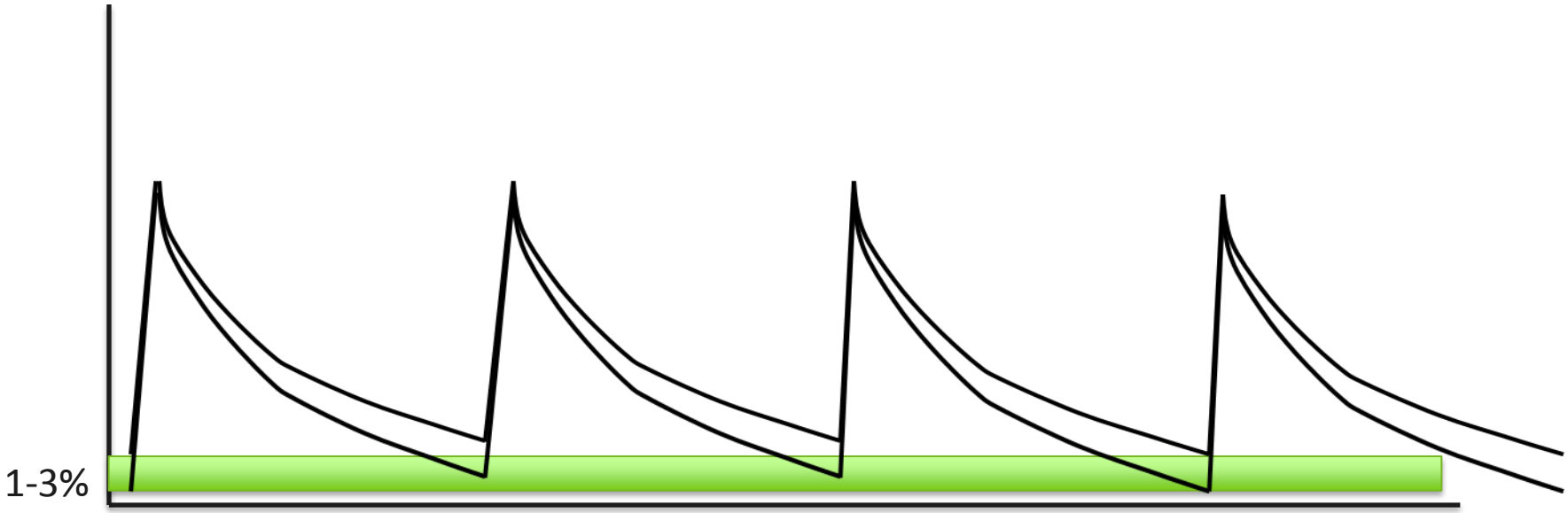
Why is there a need for other products?

- Frequent intravenous infusions are a burden
- Patients still bleed despite prophylaxis
- Risk of inhibitors is 33%
- Treatment for patients with inhibitors is less effective

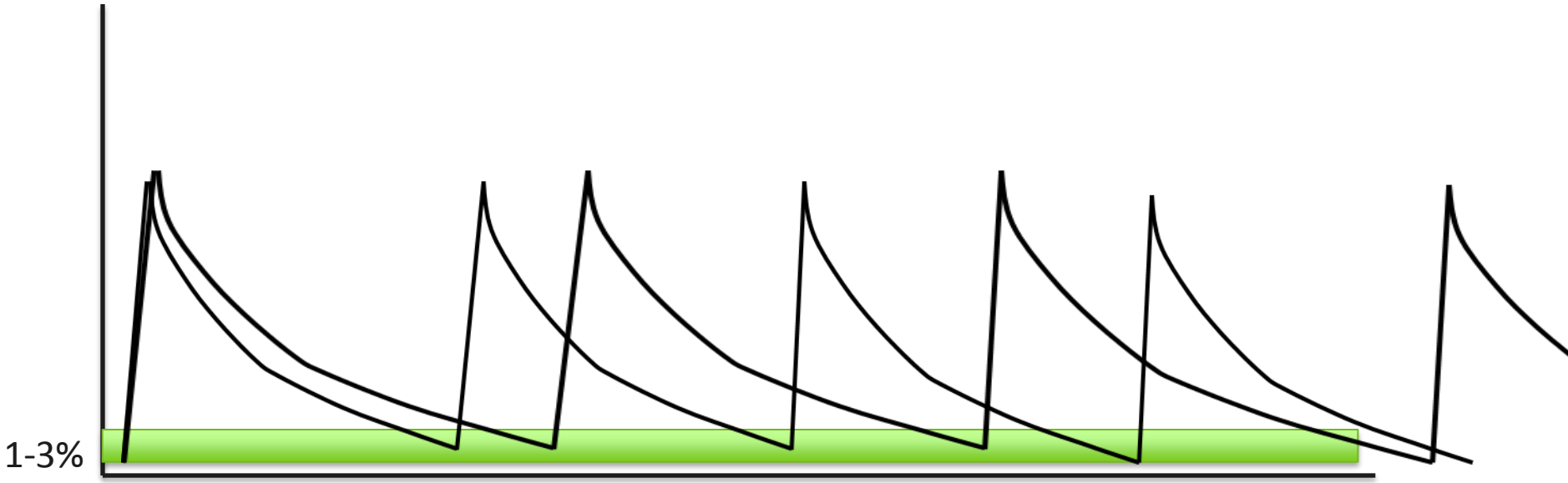


Arruda, et al. Blood 2017

Extended half life factors



Extended half life factors



Extended half life factors

FVIII

Fc fusion protein

- Efmoroctogog (Eloctate)

PEGylated protein

- Rurioctocog (Adynovate)
- Damoctogog (Bay 94-9027)
- Turoctogog (N8-GP)

FIX

Fc fusion protein

- Eftrenonacog (Alprolix)

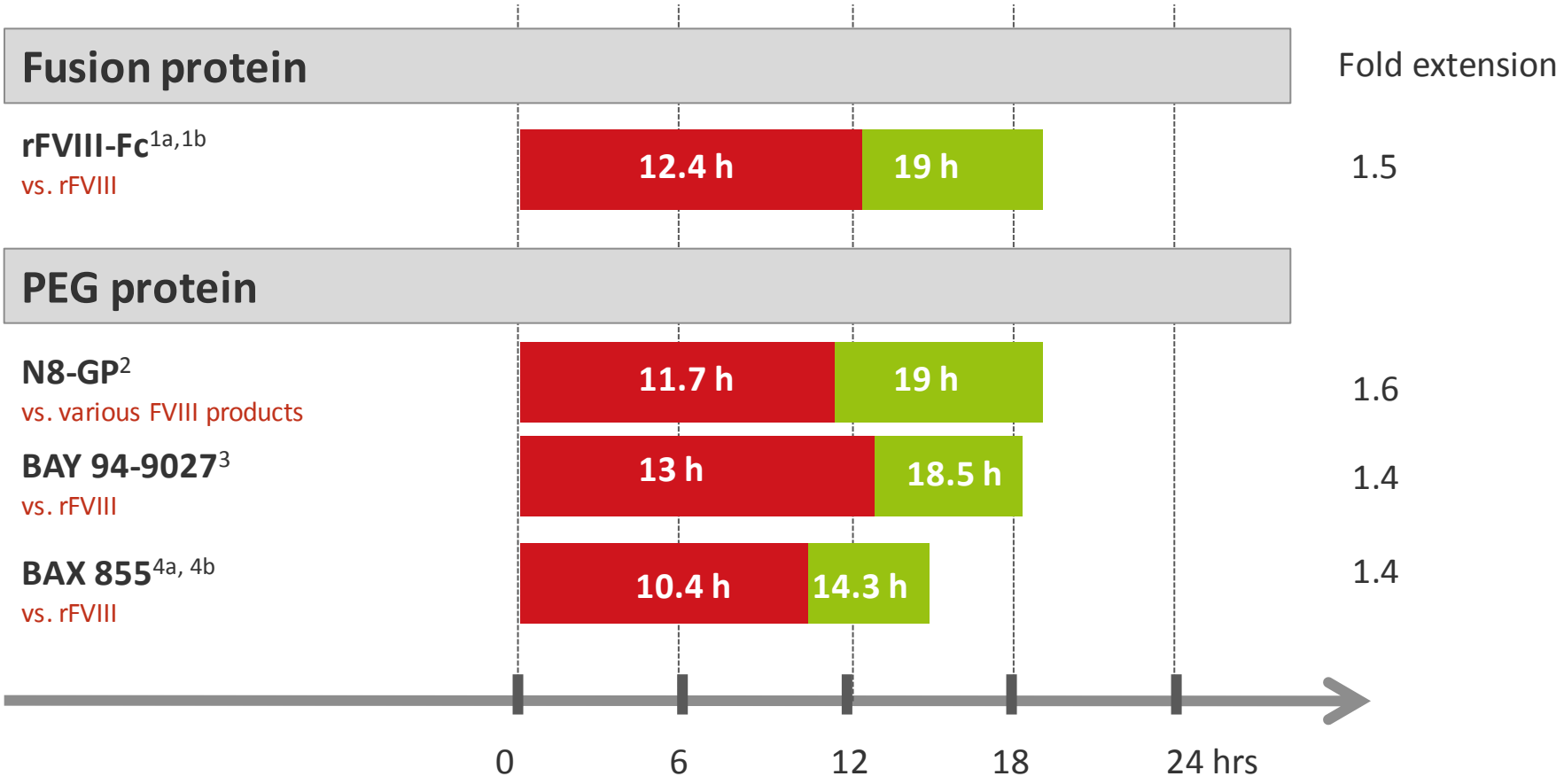
Albumin fusion protein

- Albutrepenonacog (Idelvion)

PEGylated protein

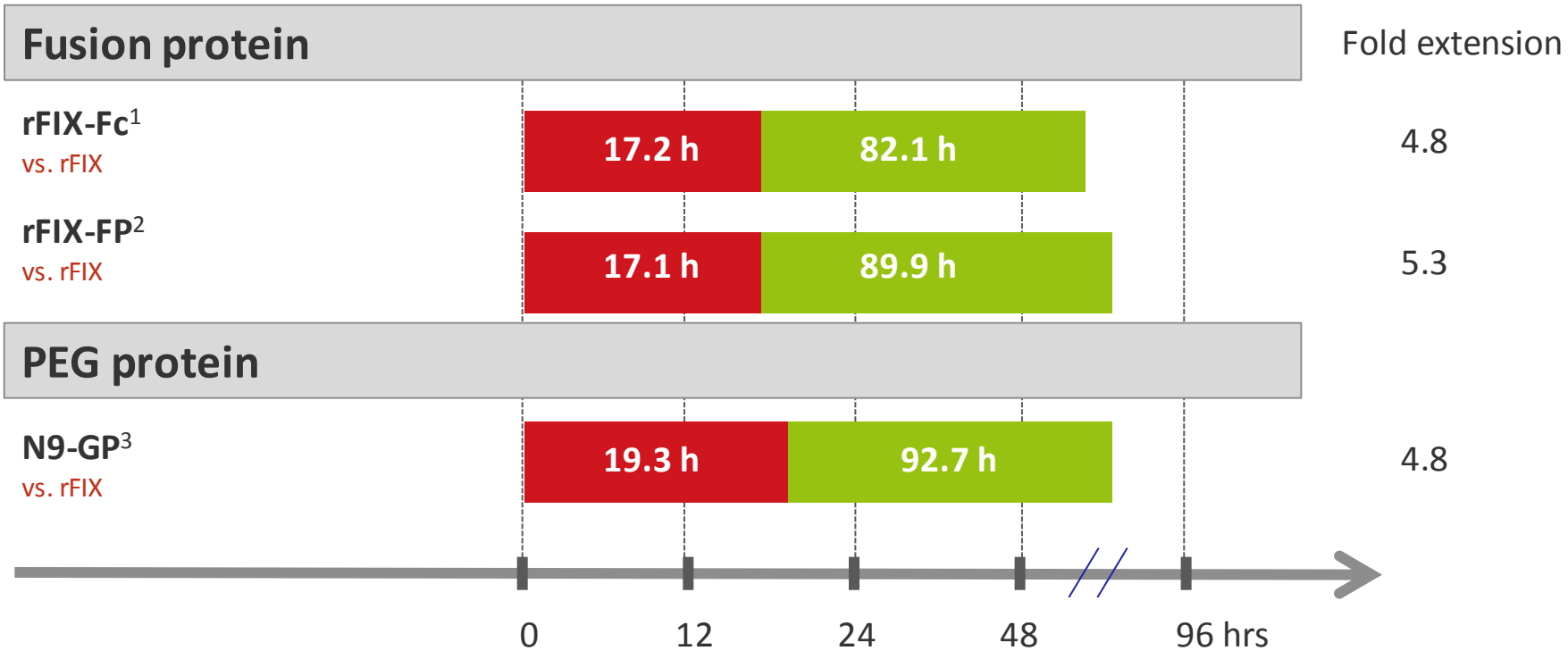
- Nonacog beta pegol (N9-GP, Rebinyn)

EHL - FVIII



1. a) Powell JS et al. *Blood* 2012; 119: 3031-7.
   b) Mahlangu J et al. *Blood* 2014; 123: 317-25.
2. Tiede A et al. J Thromb Haemost 2013; 11: 670-8.
3. Coyle TE et al. J Thromb Haemost 2014; 12: 488-96.
4. a) Konkle BA et al. *Blood* 2015; 126:1078-85.
   b) Bevan DH et al. *Haemophilia* 2013; 19 (Suppl. 2), 10-82. PO53

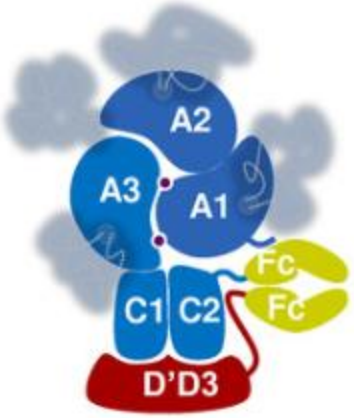
EHL-FIX



1. Powell JS et al. *N Engl J Med.* 2013;369(24):2313-23.
2. Santagostino E et al. *Blood* 2012; 120(12): 2405–11.
3. Negrier C et al. *Blood* 2011;118(10):2695-701.

Next generation EHLs

- FVIII
  - rFVIIIFc-VWF-XTEN)
  - PSA-FVIII (BAX 826)
- FIX
  - CB 2679d/ISU304



Willingness for patients to use EHLs

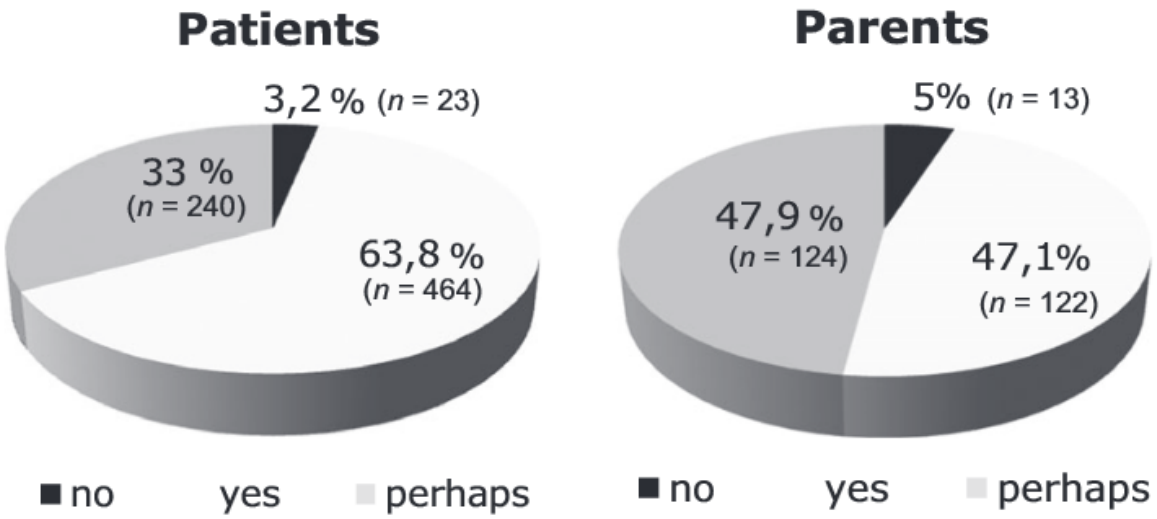


Fig. 2. Willingness to switch from current product to new extended half-life product [adult patients (n = 743), parents (n = 262)].

Von Mackensen, Haemophilia 2017

Reasons for patients to use EHLs

Table 4. Reasons to switch to new extended half-life products (adult patients, parents).

Reasons for switching (multiple answers possible)	Adults *N* (%)	Parents *N* (%)	*P*-value
Longer half-life/dosing interval of new product	555 (86.7)	192 (88.9)	*ns*
More security when travelling for a short period	405 (63.3)	123 (56.9)	*ns*
Same safety of new product	392 (61.3)	146 (67.6)	*ns*
New product advantages for surgery	335 (52.3)	97 (44.9)	*ns*
Longer stability at ambient temperatures of new product	**328 (51.3)**	**81 (37.5)**	**0.0001**
Better efficacy of new product	322 (50.3)	100 (46.3)	*ns*
New product beneficial for doing sport	**285 (44.5)**	**134 (62.0)**	**0.0001**
Easier application of new product	209 (32.7)	80 (37.0)	*ns*
Lower price of new product	134 (20.9)	54 (25.0)	*ns*
Motivated to switch to prophylaxis with new product	**100 (15.6)**	**19 (8.8)**	**0.012**
Sufficient experience in practical use	**82 (12.8)**	**47 (21.8)**	**0.001**
Other reasons	28 (4.4)	13 (6.1)	*ns*

Von Mackensen, Haemophilia 2017

Reasons for patients NOT to use EHLs

Table 5. Reasons NOT to Switch to New EHL Products (adult patients, parents).

Reasons for NOT switching (multiple answers possible)	Adults *N* (%)	Parents *N* (%)	*P*-value
Fear of inhibitor development of new product	**83 (59.7)**	**87 (87.9)**	**0.0001**
Fear of uncertain safety of new product	**77 (55.4)**	**68 (68.7)**	**0.038**
No side effects of current product	76 (54.7)	50 (50.5)	*ns*
Satisfaction with current product	68 (48.9)	36 (36.4)	*ns*
Lack of transparency of info of new product	45 (32.4)	27 (27.3)	*ns*
Good manageability of current product	33 (23.7)	17 (17.2)	*ns*
Immediate availability of current product	**33 (23.7)**	**12 (12.1)**	**0.024**
No advantage to change product	21 (15.1)	7 (7.1)	*ns*
Other reason	9 (6.5)	4 (4.0)	*ns*

Von Mackensen, Haemophilia 2017

Clinical data on switching

AHCDC:

Table 1. Per patient median factor utilization in the 6 months pre-and post-switch to EHL by IU kg $^{-1}$ week $^{-1}$*.

	Severe haemophilia A (n = 62)		Severe haemophilia B (n = 17)	
	Median, (IQR) (IU kg^{-1} week^{-1})	Range (IU kg^{-1} week^{-1})	Median (IQR) (IU kg^{-1} week^{-1})	Range (IU kg^{-1} week^{-1})
Pre-switch	101 (70; 115)	12–200	105 (64; 146)	46–235
Post-switch	82 (70; 98)	36–140	53 (48; 60)	42–94
Change	−19%	–	−50%	–

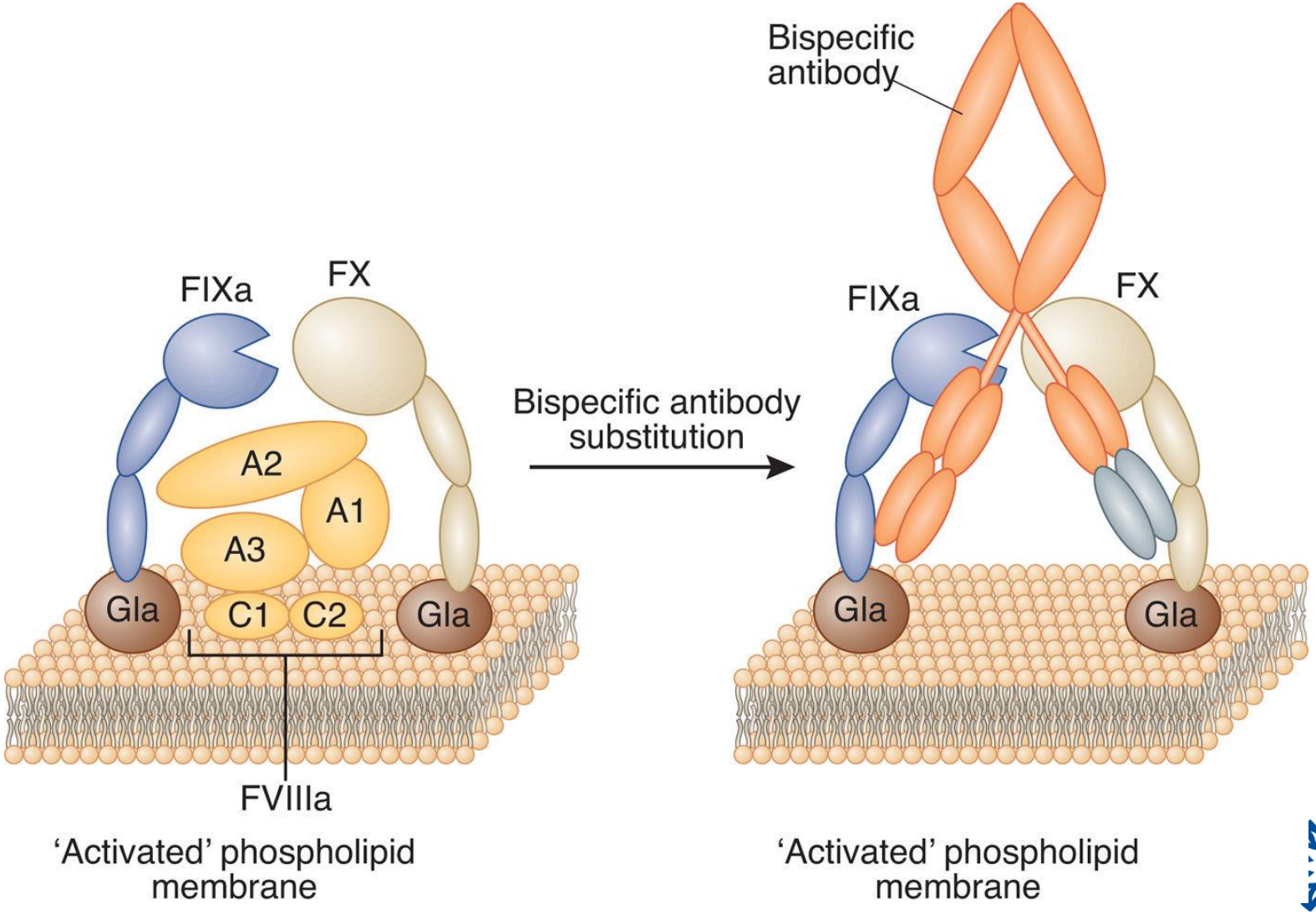
*76/79 of these cases on prophylaxis prior to switching.

Keepanasseril et al, Haemophilia 2017

Non-factor therapy

- Mimicking drugs
  - Bispecific antibody to IX/X (emicizumab; Hemlibra®)
- Suppressing clot regulators
  - Anti-TFPI (concizumab)
  - RNA interfering antithrombin (fitusiran; ALN-AT3)
- Gene therapy

Emicizumab


Bispecific antibody
FIXa
FX
A2
A1
A3
Gla
C1
C2
Gla
FVIIIa
'Activated' phospholipid membrane
Bispecific antibody substitution
FIXa
FX
Gla
Gla
'Activated' phospholipid membrane

Emicizumab in inhibitor patients: HAVEN1

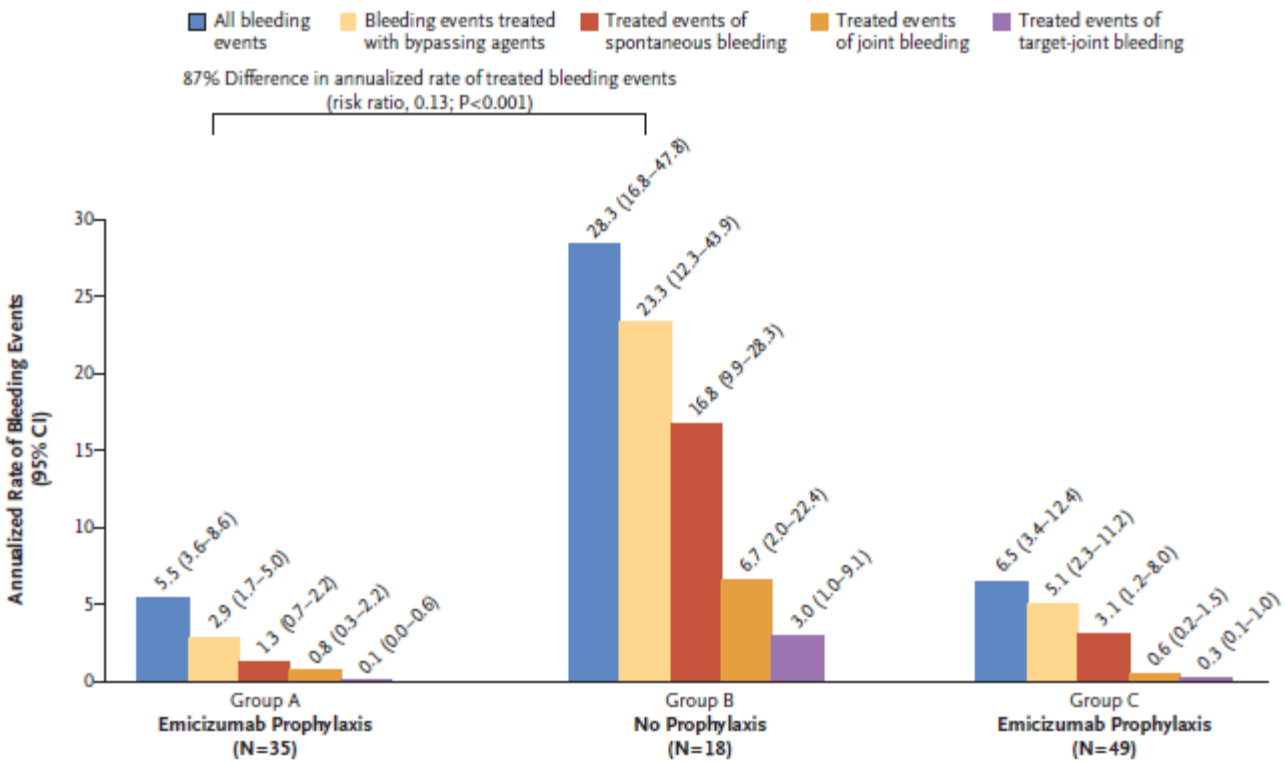


Figure 1. Annualized Bleeding Rate in Trial Groups A, B, and C.

The annualized bleeding rate was calculated with the use of a negative binomial-regression model. Participants in groups A and B had previously received episodic treatment with bypassing agents; participants in group C had previously received prophylaxis with bypassing agents. Group D was not included in the current analysis owing to the short follow-up at the time of data cutoff.

Oldenburg et al, NEJM 2017

Emicizumab in inhibitor patients: HAVEN1

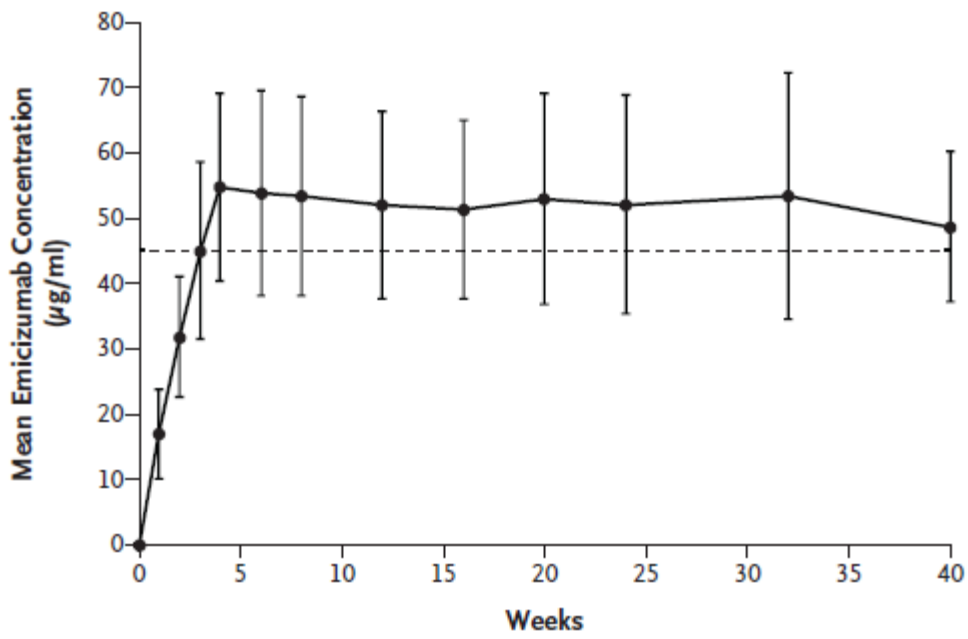


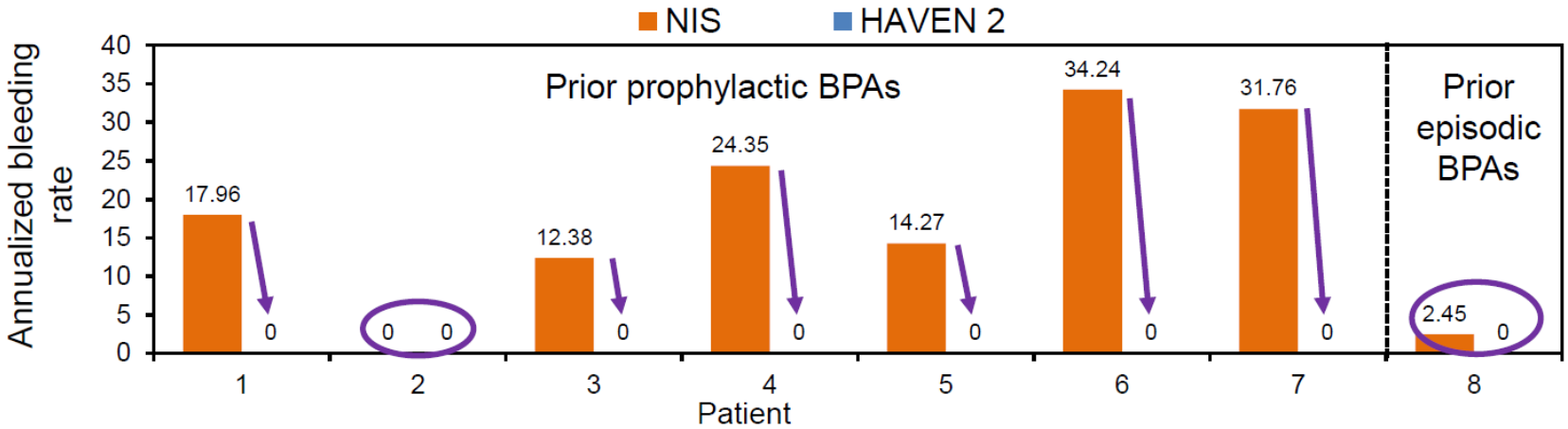
Figure 3. Observed Trough Plasma Concentrations of Emicizumab over Time with Once-Weekly Dosing (102 Patients).

As determined by pharmacokinetic and pharmacodynamic modeling, emicizumab doses of 1.5 mg per kilogram of body weight per week were predicted to result in trough plasma concentrations of emicizumab of 45 μg per milliliter (dashed line). I bars indicate standard deviations.

Oldenburg et al, NEJM 2017

Emicizumab: HAVEN2

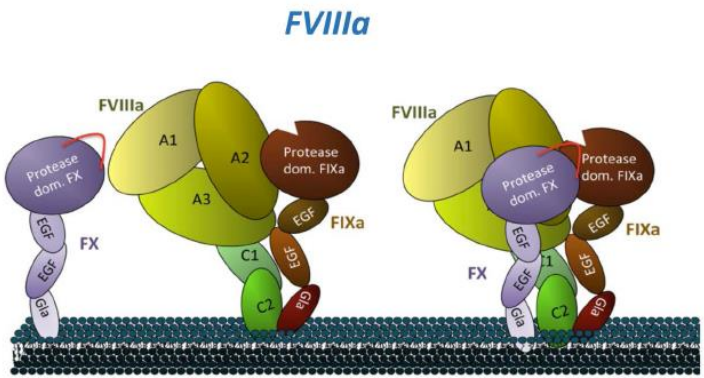
HAVEN 2 intra-individual comparison
Emicizumab prophylaxis vs prior BPA treatment

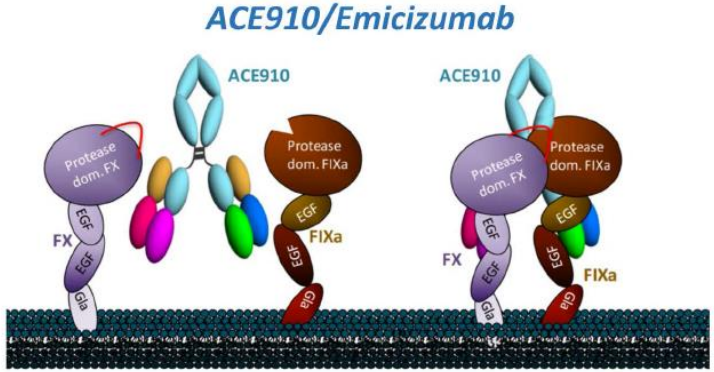


No. of treated bleeds (NIS/HAVEN 2)	6	0	0	0	4	0	8	0	5	0	12	0	12	0	1	0
Follow-up (days) (NIS/HAVEN 2)	122	99	61	99	118	89	120	86	128	85	128	85	138	85	149	99

- Intra-individual comparison performed for 8 NIS patients on HAVEN 2 study ≥12 weeks
- Zero bleeds reported for all 8 patients receiving emicizumab (efficacy period 85–99 days)
- Substantial reductions in treated bleed rates with emicizumab prophylaxis vs prior BPA treatment

Emicizumab



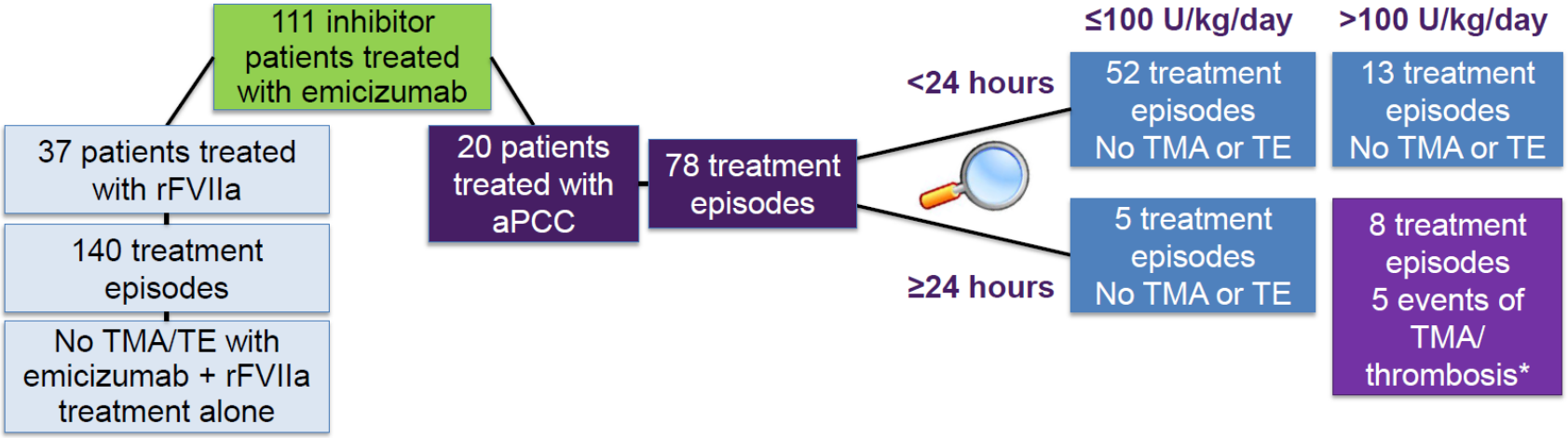


Multiple sites of interaction	Single sites of interaction
High affinity for enzyme & substrate *(low to high nanomolar range)*	Low affinity for enzyme & substrate *(micromolar range)*
Specific for FIXa and FX *(no binding to FIX and FXa)*	No distinction between zymogen and enzyme *(FIX vs FIXa and FX vs FXa)*
Full cofactor activity - *promotes phospholipid binding* - *stabilizes FIXa active site* - *bridges FIXa to FX*	Partial cofactor activity - *bridges FIXa to FX*
Enzyme and substrate are in excess over cofactor	Antibody is in excess over enzyme and substrate
FVIIIa has on/off mechanism	Emicizumab has no on/off mechanism
High level of self-regulation	Low level of self-regulation

Lenting et al, Blood 2017

Emicizumab

HAVEN 1 updated data
Assessment of interaction between emicizumab and aPCC

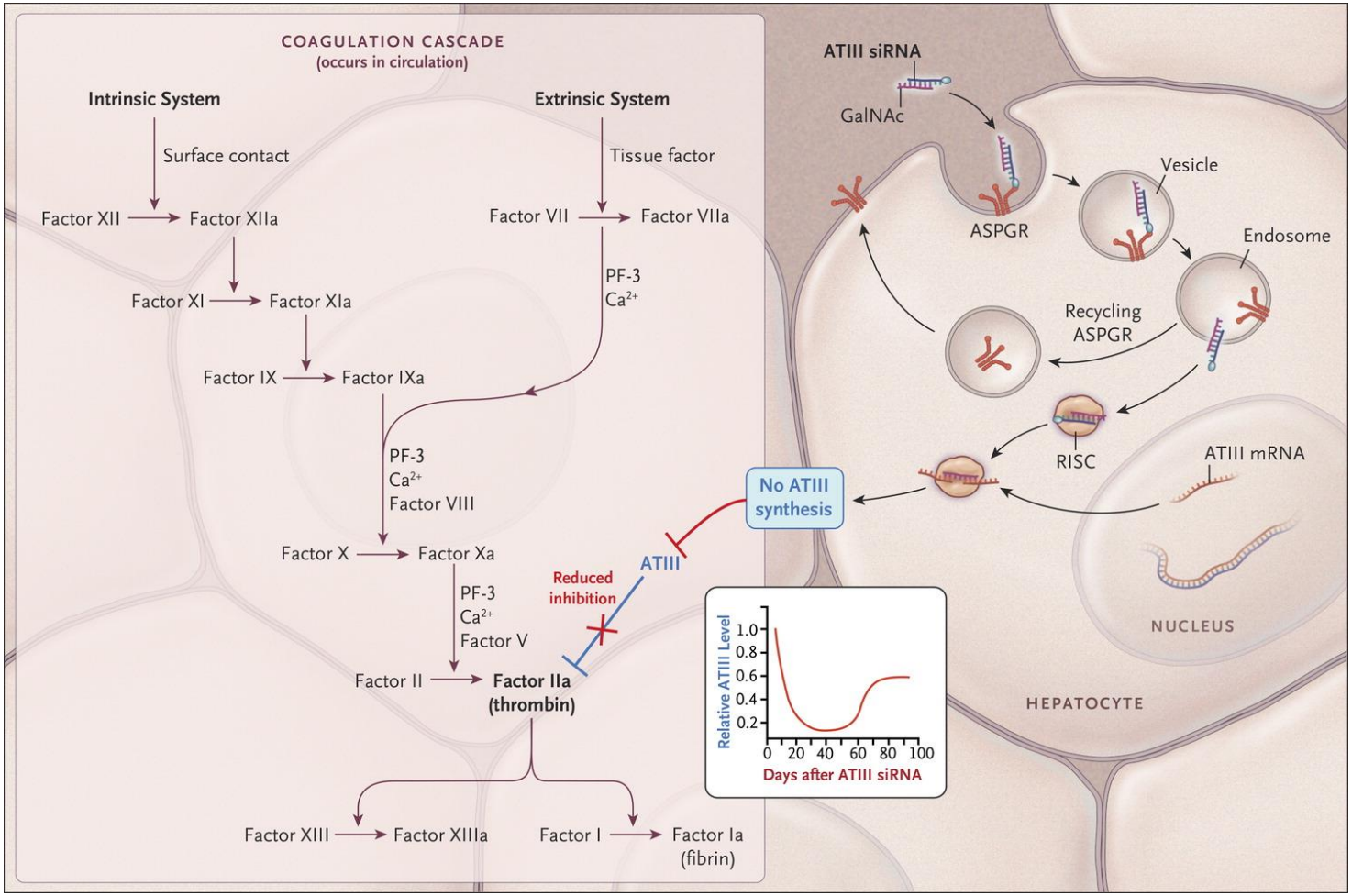


- TMA/thrombotic events only occurred with aPCC treatment averaging >100 U/kg daily for ≥24 hours
- aPCC contains activated and non-activated coagulation factors, including FII, FVII, **FIX** and **FX**, which can accumulate with repeat dosing
- Risk may be mitigated with clear dosing guidance
- No further SAEs of TE/TMA in >350 patients treated in emicizumab development program to date

*Two patients also received rFVIIa prior to/during the event.
TE, thromboembolism.

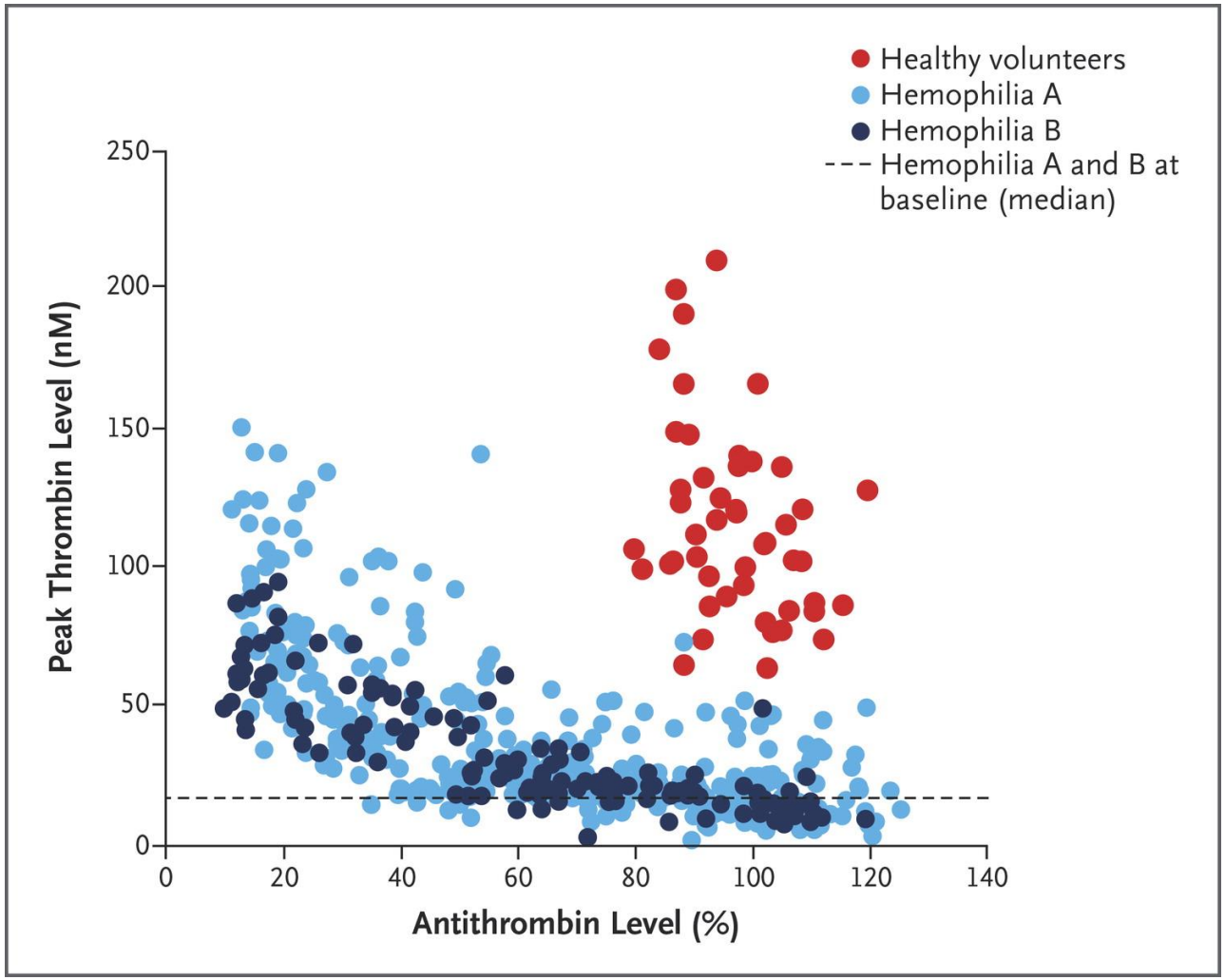
Updated data cutoff – April 21, 2017, including 8 additional patients.

Fitusiran



Ragni, NEJM 2015

Fitusiran



Pasi, NEJM 2017

Fitusiran

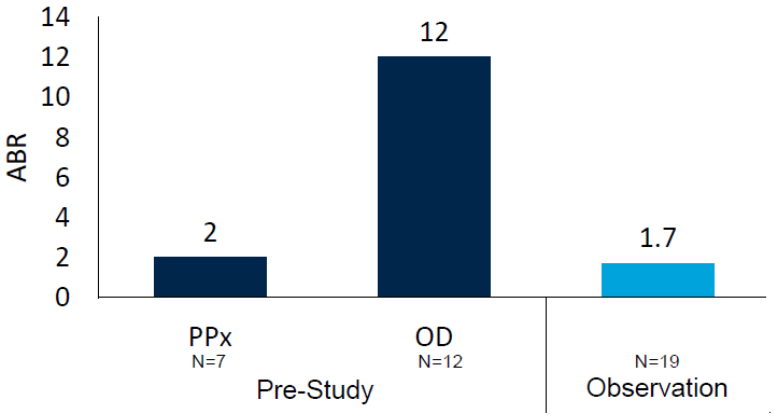
Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*

Exploratory Analysis of Bleed Events

Summary of Median ABRs in all Patients

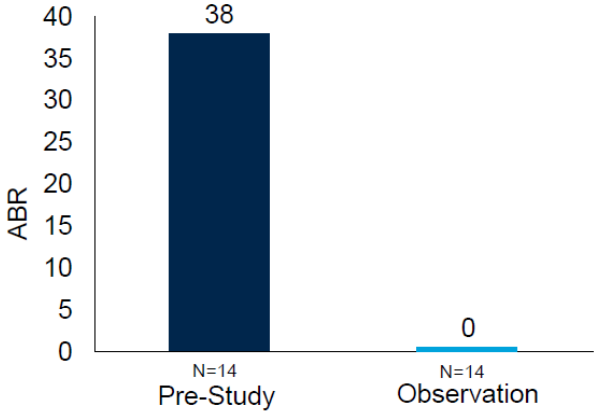
- 48% (16/33) of patients bleed free during observation period†
  - Overall median ABR in observation period = 1 (IQR: 0-3)
- 67% (22/33) of patients reported no spontaneous bleeds
  - Overall median AsBR in observation period = 0 (IQR: 0-2)

Summary of Median ABRs in Patients without Inhibitors



- Median duration in observation period: 13 months [range: 2 –19]
- Mean AT activity in observation period (relative to baseline): 22%

Summary of Median ABRs in Patients with Inhibitors



- Median duration in observation period: 6 months [range: 1 –11]
- Mean AT activity in observation period (relative to baseline): 18%

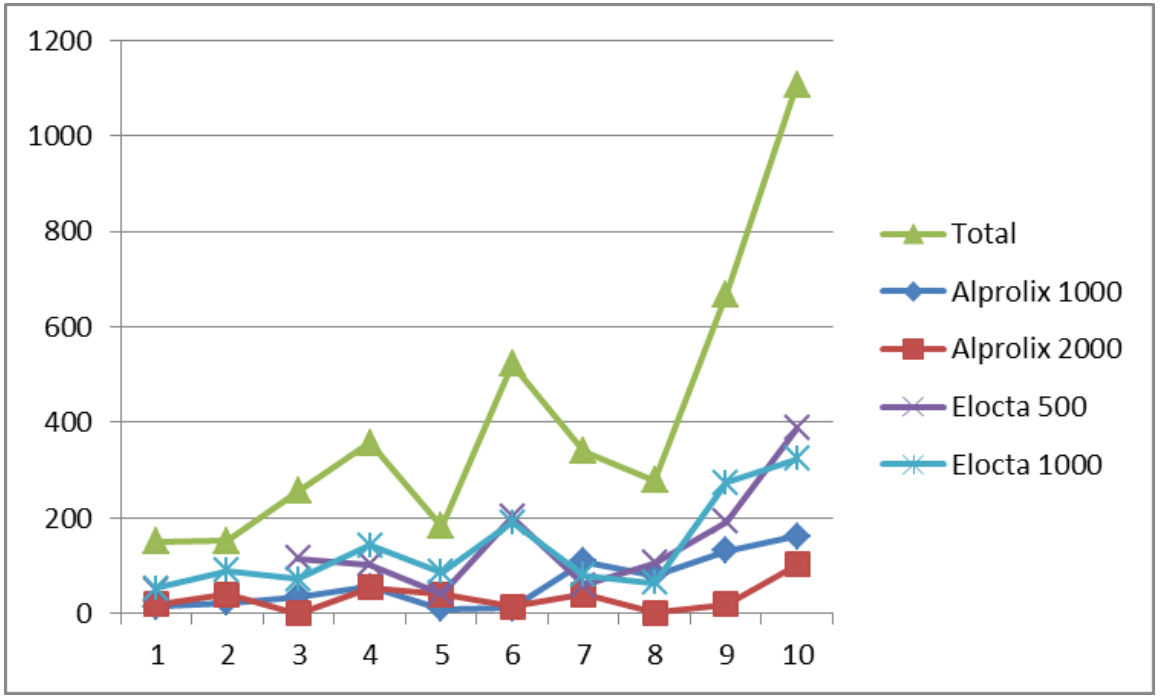
Fitusiran

- 1 patient (27y) died due to a cerebral venous sinus thrombosis after treatment with FVIII for a hip bleed

How do we currently make the choice?

- When do we switch to an EHL product?
  - Patient perspectives:
    - Bleeding rates
    - Venous access
    - Convenience
  - Center perspectives:
    - Costs

Alprolix and Elocta use 2017 in Utrecht



Conclusion