Haemophilia A with moderate/severe phenotype and prophylaxis

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My disclosures

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Employee	None
Shareholder	None

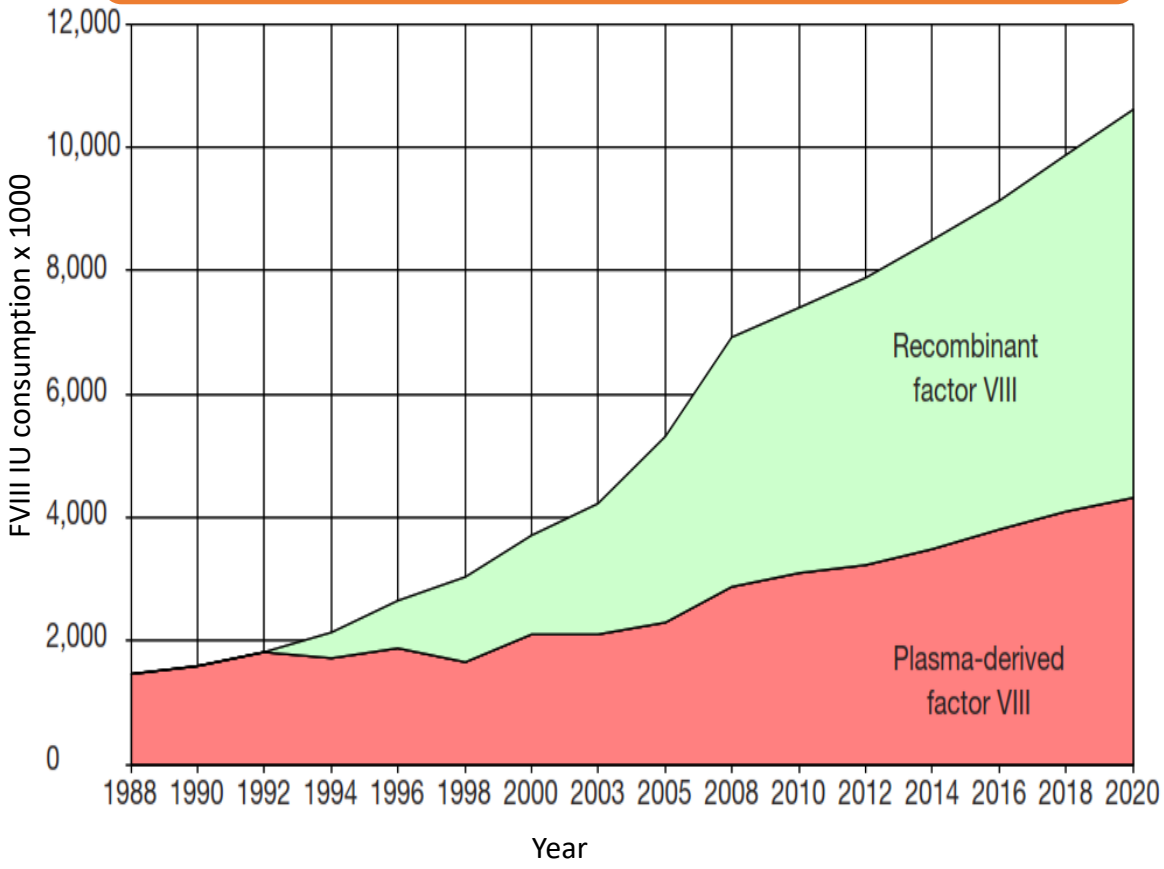
Agenda

- Treatment paradigm in mild, moderate and severe haemophilia patients
- Unmet needs in the treatment of haemophilia with moderate/severe phenotype
- Latest data on the management of haemophilia with moderate/severe phenotype
- Concluding remark

Unprecedented increase in replacement haemophilia therapies

- **1840** • 1st successful blood transfusion[1]
- **1954** • 1st patient treated with porcine plasma FVIII[1]
- **1964** • 1st use of Cryoprecipitate[2]
- **1970** • Frozen plasma derived clotting factor available[1]
- **1989** • 1st use of recombinant Clotting factor[1]
- **1998** • 1st use of extended half-life clotting factor[3]
- **2017** • 1st use of non-factor therapy[4]

Global FVIII consumption

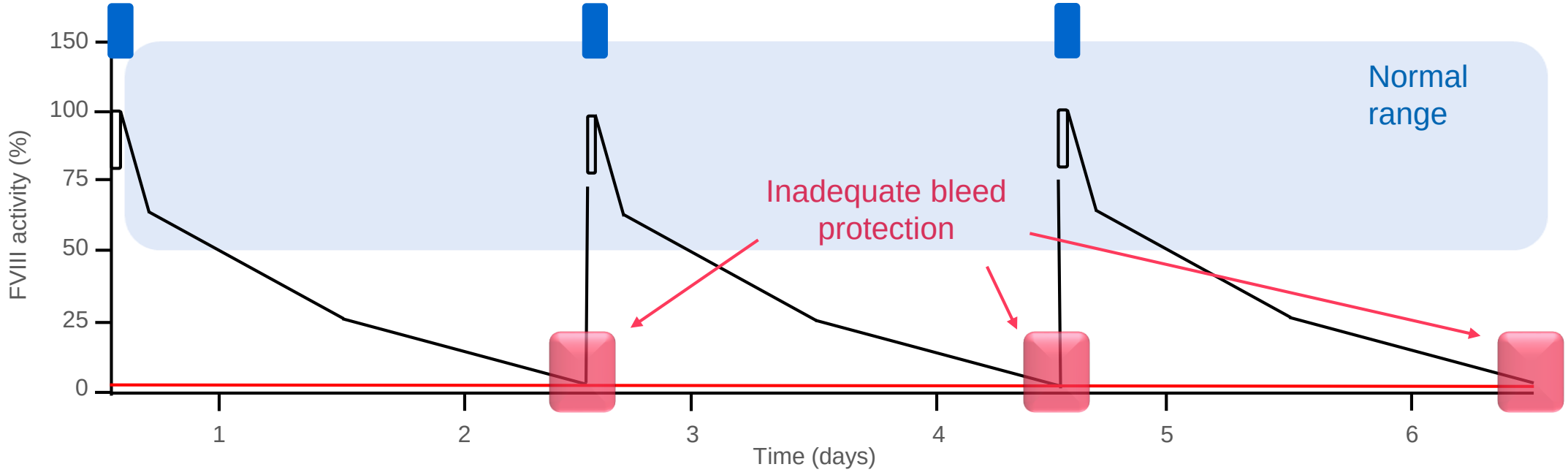


1. Lee C, et al. Textbook of haemophilia Third edition, Chichester, Wiley Blackwell, 2014;
2. Pool J, et al. NEJM 1965;273:1443–7;
3. Powell J et al. Blood 2012;19:3031–7;
4. Oldenburg et al NEJM 2017, 377(9): 809-818
5. M. Hotchko and P. Robert Annals of Blood 2018; 3(2)1-6

There is inconsistent protection by replacement therapies.

	Standard half-life product[1,2]
Haemophilia A	25 - 40 IU/kg IV FVIII 3 x week minimum

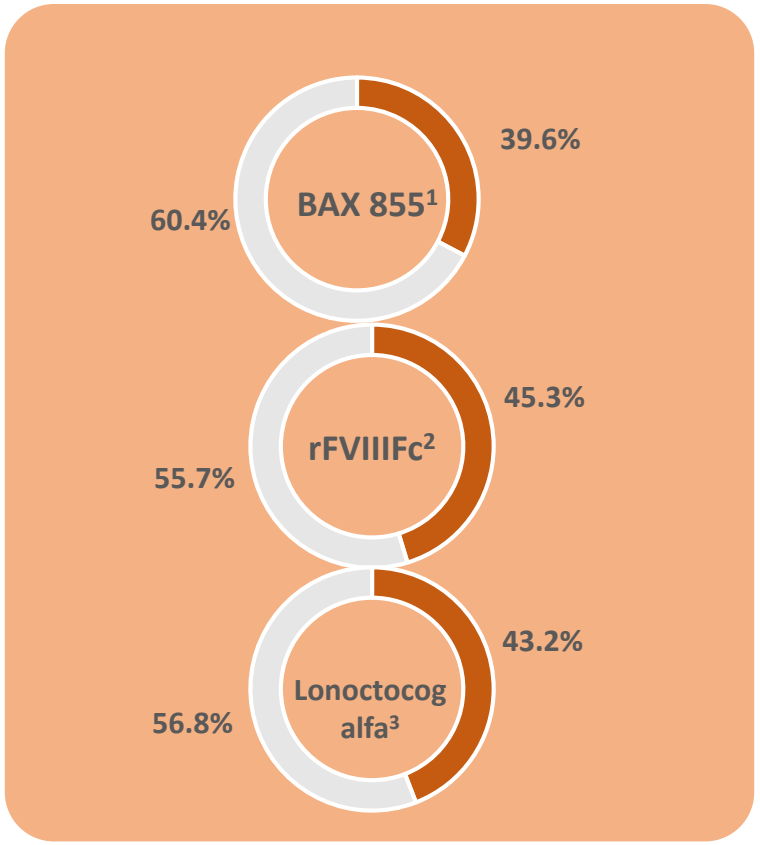
	Extended Half-life product [3,4]
Haemophilia A	25-65 IU/kg IV FVIII 1-2 x week



1. Nilsson IM et al. *J Int Med* 1992; 232:25-32; 2. Löfqvist T et al. *J Int Med* 1997; 241:395-400; 3 Mahlangu 2021 Expert review on Pharmacotherapy; 4 Mahlangu Ther Adv Hematol 2018, 9(11):335-346; Jimenez-Yuste V, et al. Blood Transfus 2014

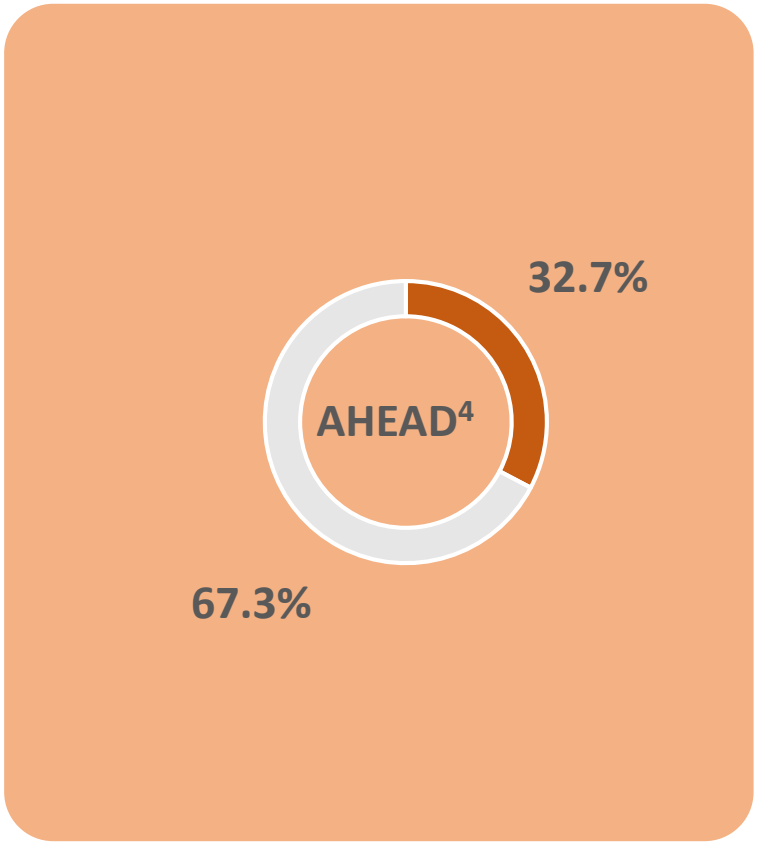
Zero bleed rates are low on replacement prophylaxis

Clinical Trials



Zero treated bleeds
≥1 treated bleed

Real-world experience

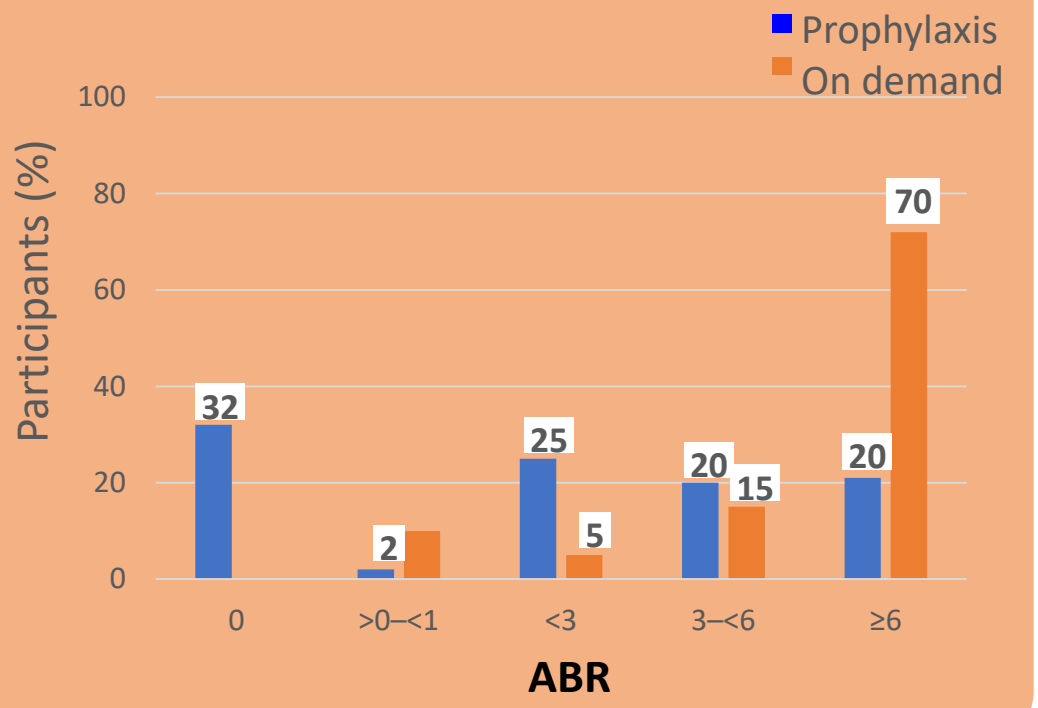


AHEAD- Advate in haemophilia A outcome database

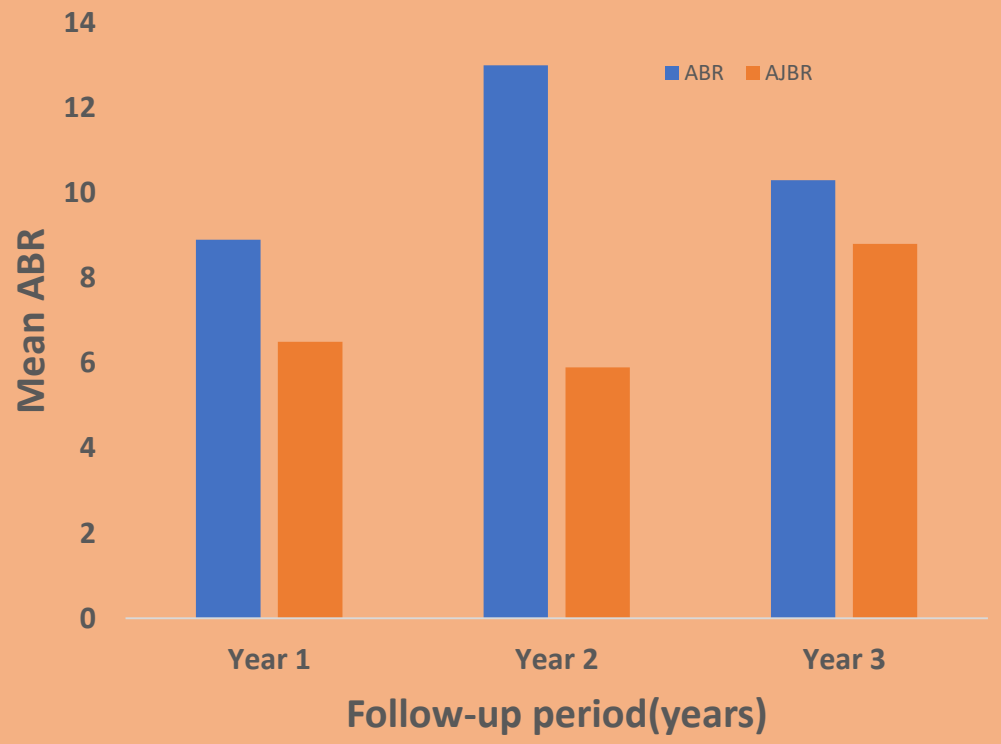
1. Konkle BA, et al. Blood 2015;126:1078–85; 3. Mahlangu J, et al. Blood 2014;123:317–25; 4. Prescribing information. Available at: http://labeling.cslbehring.com/PI/US/Afstyla/EN/Afstyla-Prescribing-Information.pdf. 4. Khair K, et al. Haemophilia 2018;24:85–96; 2

Real-world bleed rates are high in haemophilia :
AHEAD study

ABR by percentage of study participants[1]



ABR over 3 years in the AHEAD study

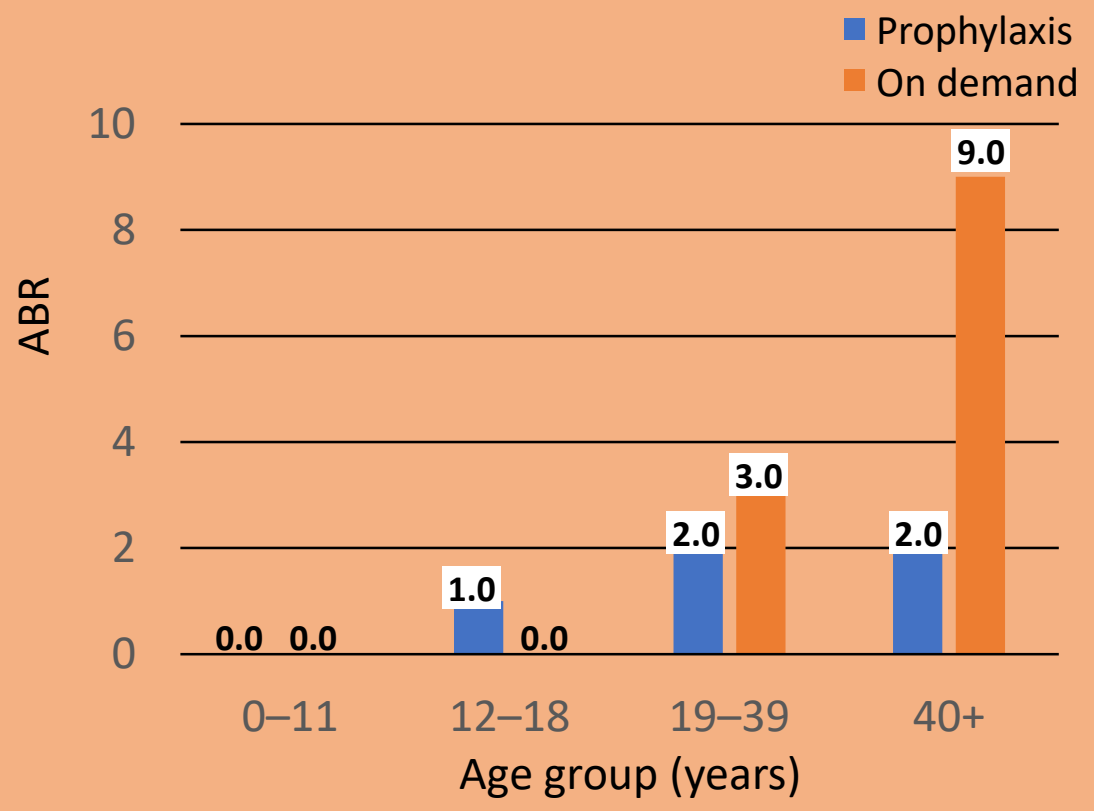


Kair et al Haemophilia. 2018;24:85–96;

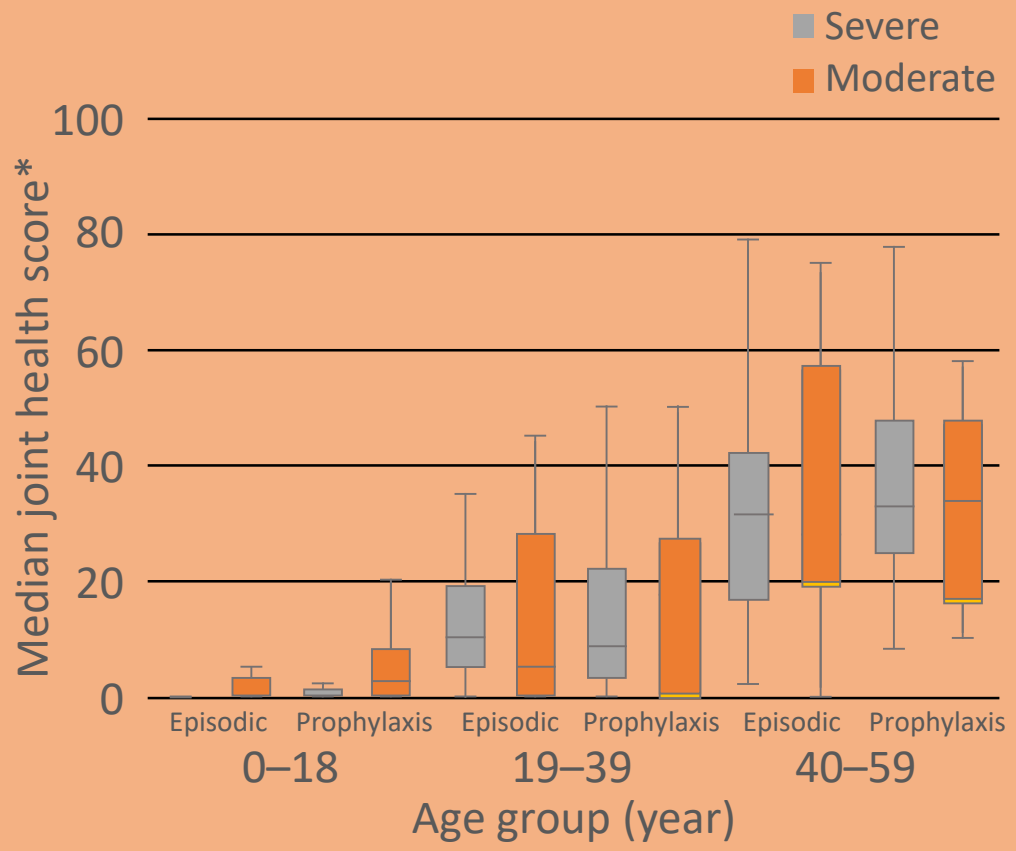
Real-world bleeds lead to joint damage.

Thunder study

Joint bleed ABR in people with severe haemophilia A without FVIII inhibitors[1]



Joint Health Score* by age, severity and treatment regimen[1]

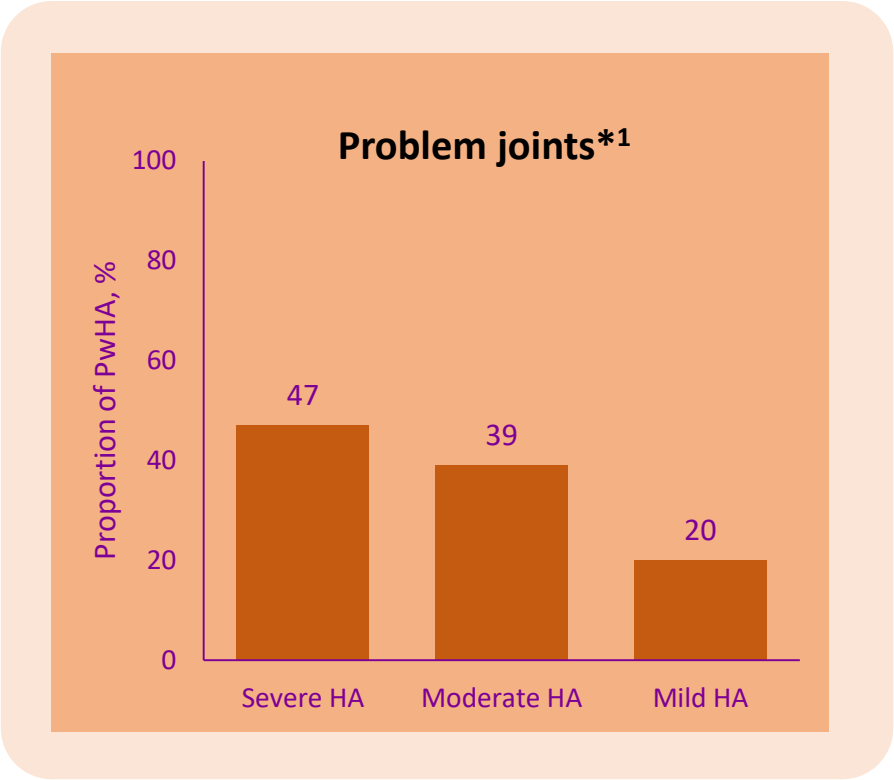


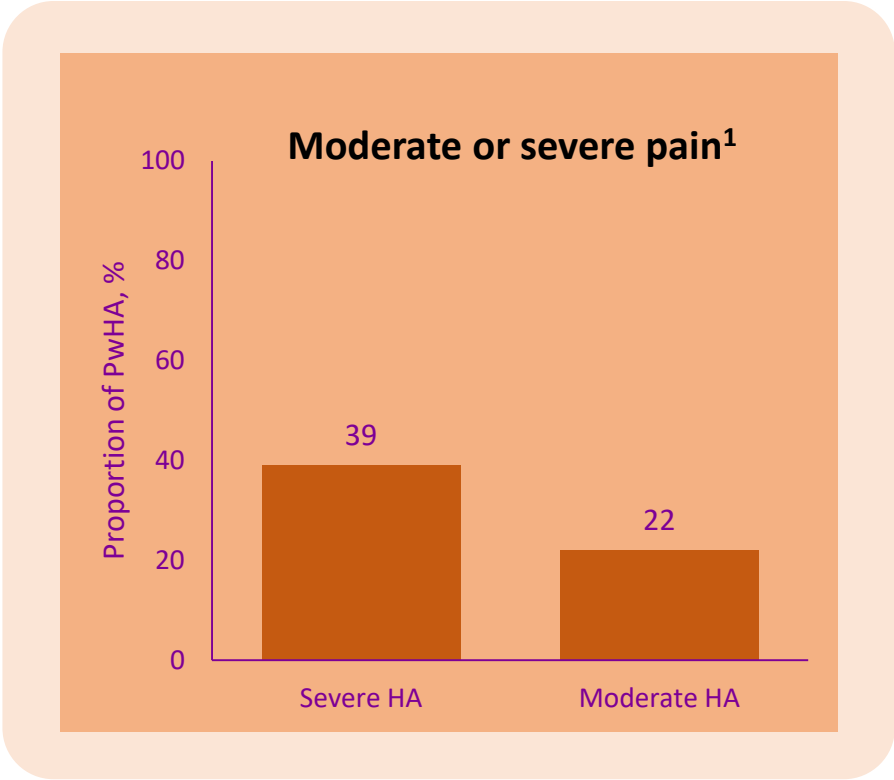
*Higher scores are indicative of poorer joint health. Scores derived from National Haemophilia Database records.

1. Scott MJ, et al. Haemophilia 2019;25:205–212.

Arthropathies are across all severities of haemophilia

CHESS II study[1]





As few as two or three joint bleeds may cause irreversible joint damage and impact quality of life[2]

*defined as any joint that has been permanently damaged as a result of a bleeding disorder, with or without persistent bleeding
CHESS, Cost of haemophilia in Europe: a Socioeconomic Survey; HA, hemophilia A; PwHA, people with hemophilia A

1. Noone D et al. Presented at ASH 2020; Abst. 3449;
2. Gringeri A et al. haemophilia 2014;20(4):459–63.

Bleeding outcomes in non-inhibitor patients-
systemic review

	No. of cohorts	Sample size	Median (IQR)	Pooled estimated mean (95% CI)
Interventional studies				
(n = 48)				
Overall ABR	67	3588	3.1 (2.2–4.8)	**3.4 (3.0–3.7)**
Joint ABR	25	1540	1.5 (1.1–2.4)	**2.0 (1.6–2.5)**
Proportion with zero bleeding events	**37**	**2312**	**39.6 (27.1–48.0)**	**38.5 (33.1–43.9)**

	No. of cohorts	Sample size	Median (IQR)	Pooled estimated mean (95% CI)
Observational				
(n = 10)				
Overall ABR	29	2244	4.9 (3.5–7.2)	**4.8 (4.0–5.5)**
Joint ABR	21	1423	2.4 (1.7–4.7)	**2.6 (2.1–3.2)**
Proportion with zero bleeding events	**16**	**1646**	**27.0 (10.9–32.2)**	**21.8 (19.9–47.5)**

Mannucci et al. Haemophilia 2023(29):954-962

Prophylaxis with Non-factor therapies may improve outcomes

Class	Molecule	Sponsor	Phase of development
FVIII Mimetic	Emicizumab[1,2,3,4]	Roche	Phase 3 completed + ongoing other studies
	Denecimig(Mim8)	Novo Nordisk	Phase 3 ongoing
Anti-thrombin	Fitusiran[5,6]	Sanofi	Phase 3 completed
Anti-TFPI	Concizumab[7]	Novo Nordisk	Phase 3 completed
	Marstacimab[8]	Pfizer	Phase 3 ongoing
	Befovacimab	Bayer	Terminated in Phase 1
	MG1113	Greencross	Phase 1 ongoing
Anti-APC	Serpin PC	Abcintex	Phase 1 ongoing

1.Oldenberg etal N Eng J Med 2017:377:809-18 2. Young et al Blood 2019 ; 3. Mahlangu NEJM 2018 4. Pipe Lancet haematology 2019; 5. Young et al Lancet. 2023 Mar 29:S0140-6736(23)00284-2. 6 Srivastava et al. Lancet Haematol. 2023 Mar 29:S2352-3026(23)00037-6 7. Chowdary et al JTH 2015; 13: 743–54 ; 8. Mahlangu ISTH 2019.

Emicizumab clinical development programmes is comprehensive - several completed phase 3 studies

Clinical Program	Publication communication	Population	Haemophilia A phenotype	Enrolled Participants (751)	Dosing regimen
Haven 1	Oldenburg et al. 2017	Adolescent and adult	Inhibitor	113	1.5 mg/kg Q week
Haven 2	Young et al. 2019	Paediatric	Inhibitor	88	1.5 mg/kg Q week 3.0 mg/kg Q2 weeks 6 mg/kg Q4 weeks
Haven 3	Mahlangu et al. 2019	Adolescent and adult	Non inhibitor	152	1.5 mg/kg Q week 3.0 mg/kg Q2 weeks
Haven 4	Pipe et al. 2019	Adolescent and adult	Inhibitor and no inhibitor	48	6.0 mg/kg Q4 weeks
HoHoemi	Shima et al. 2019	Paediatric	Non inhibitor	13	3.0 mg/kg Q2 weeks 6.0 mg/kg Q4 weeks
Haven 5	Yang et al. 2022	Paediatric	Inhibitor	70	1.5 mg/kg Q week 6.0 mg/kg Q4 weeks
STASEY	Jemenez-Juste et al. 2022	Adolescent and adult	Inhibitor and non inhibitor	195	3.0 mg/kg Q2 weeks 6.0 mg/kg Q4 weeks
Haven 6	Negrier et al. 2023	All age groups	Non-inhibitor	72	1.5 mg/kg Q week 3.0 mg/kg Q2 weeks 6 mg/kg Q4 weeks

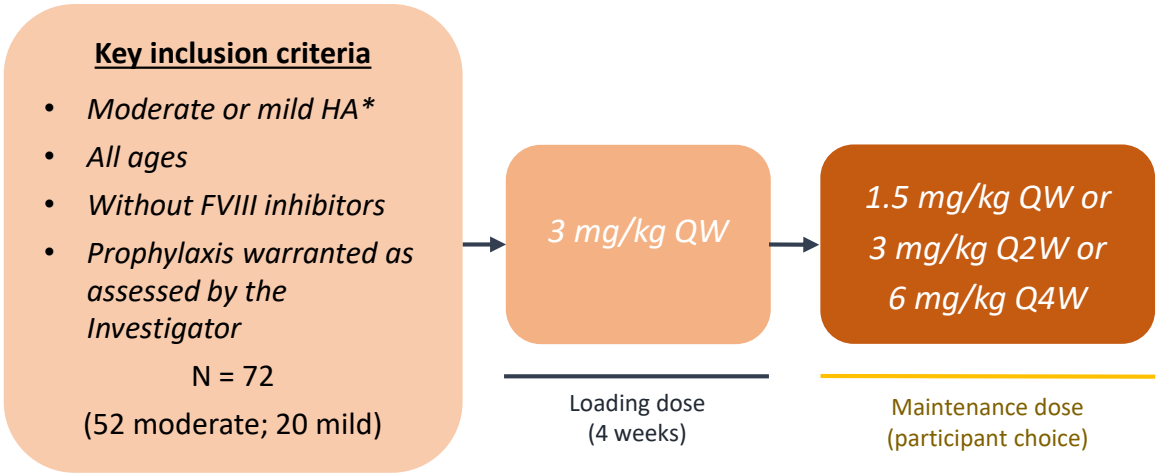
Haven 6 study

Emicizumab in people with moderate or mild haemophilia A (HAVEN 6): a multicentre, open-label, single-arm, phase 3 study

Claude Négrier, Johnny Mahlangu, Michaela Lehle, Pratima Chowdary, Olivier Catalani, Ronald J Bernardi, Víctor Jiménez-Yuste, Benjamin M Beckermann, Christophe Schmitt, Giuliana Ventriglia, Jerzy Windyga, Roseline d'Oiron, Paul Moorehead, Sunita Koparkar, Vanda Teodoro, Amy D Shapiro, Johannes Oldenburg, Cedric Hermans

Negrier et al Lancet Haematology 2023; 10: e168-177

HAVEN 6 study design and methodology



*Moderate HA (FVIII level ≥1%–≤5%), mild HA (FVIII level >5%–<40%); †one participant with moderate HA was enrolled but withdrew prior to treatment.
ABR, annualised bleeding rate; AE, adverse event; CATCH, comprehensive assessment tool of challenges in haemophilia; EmiPref, emicizumab preference; F, factor; HA, haemophilia A; HJHS, haemophilia joint health score 2.1; PD, pharmacodynamics; PK, pharmacokinetics; PwHA, people with haemophilia A; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event; TE, thromboembolic event; TMA, thrombotic microangiopathy

- HAVEN 6 is a Phase III, multicentre, single-arm, open-label study of emicizumab prophylaxis in people with **moderate or mild** HA **without** FVIII inhibitors
- Safety endpoints were
  - AEs, SAEs,
  - AEs of special interest (including **TEs** and **TMAs**) and drug discontinuation due to AEs
- Efficacy endpoints were:
  - Negative binomial regression model estimates of **ABR** for **treated bleeds**, all bleeds, and joint/target joint/ spontaneous bleeds
  - change from baseline in **HJHS**
- Other endpoints include:
  - **PK**, **PD**, and **immunogenicity**
  - health-related quality of life using **CATCH**
  - Treatment preference as measured by the **EmiPref** questionnaire

Negrier et al Lancet Haematology 2023; 10: e168-177

Baseline characteristics

	Study population (N = 72)
Median (range) age, years	23.0 (2.0–71.0)
Gender, n (%)	
Male	69 (97.2)
Female*	2 (2.8)
Ethnicity,† n (%)	
Asian	3 (4.2)
Black or African American	6 (8.5)
White	60 (84.5)
Unknown	2 (2.8)
Haemophilia severity,‡ n (%)	
Mild	21 (29)
Moderate	51 (71)

	Study population (N = 72)
Current treatment regimen,§ n (%)	
Prophylactic	37 (52.1)
Episodic	34 (47.9)
History of FVIII inhibitors, n (%)	1 (1.4)
Number of bleeds in the past 24 weeks	
Mean (SD)	3.4 (7.5)
Median (range)	2.0 (0–60)
With target joints at baseline, n (%)	24 (33.8)
Number of target joints at baseline	
Mean (SD)	0.6 (1.2)
Median (range)	0.0 (0–8)

*Mild HA, n = 1; moderate HA, n = 1; these participants were classed as having HA as their FVIII levels were <40%;[1] †self-declared; ‡HA severity was defined based on the ISTH classification system where a FVIII level >5%–<40% of normal level is considered to be mild disease and ≥1%–≤5% of normal level is considered to be moderate disease;[2] §the indications for warranting prophylaxis included having a history of frequent bleeding (n = 39 [54.9%]), a history of frequent joint bleeding (n = 32 [45.1%]), a history of severe bleeding (n = 15 [21.1%]), prevention of traumatic bleeds (n = 9 [12.7%]), and other (n = 5 [7.0%]); participants may have had multiple reasons for warranting prophylaxis. As per inclusion criteria, the need/reason for warranting prophylaxis is based on investigator assessment.

HA, haemophilia A; F, factor; ISTH, International Society on Thrombosis and Haemostasis; SD, standard deviation.

Negrier et al Lancet Haematology 2023; 10: e168-177

No new safety signals were identified

AE	Participants (N=72)
Total number of AEs, n	**248**
Participants with ≥1 AE, n (%)	
Any AE	60 (83.3)
AE with fatal outcome	0 (0)
AE leading to withdrawal from treatment	0 (0)
AE leading to dose modification/interruption	0 (0)
Grade ≥3 AE	4 (5.6)
Treatment-related AE*	15 (20.8)
Injection-site reaction	12 (16.7)
Total number of SAEs,† n	10
Participants with ≥1 SAE, n (%)	8 (11.1)
AE of special interest, n (%)	
Systemic hypersensitivity/anaphylactic/anaphylactoid reaction	0 (0)
Thromboembolic event‡	1 (1.4)
Thrombotic microangiopathy	0 (0)

- Headache was the most common AE, reported for 14.1% of participants
- The majority of participants (84.5%) did not report an AE considered emicizumab-related by the Investigator
- Emicizumab-related local injection-site reactions were reported for nine participants (12.7%)
- One participant (1.4%) experienced two Grade ≥3 AEs; neither were considered emicizumab-related*
- Four participants (5.6%) reported a total of six SAEs; none were considered emicizumab-related

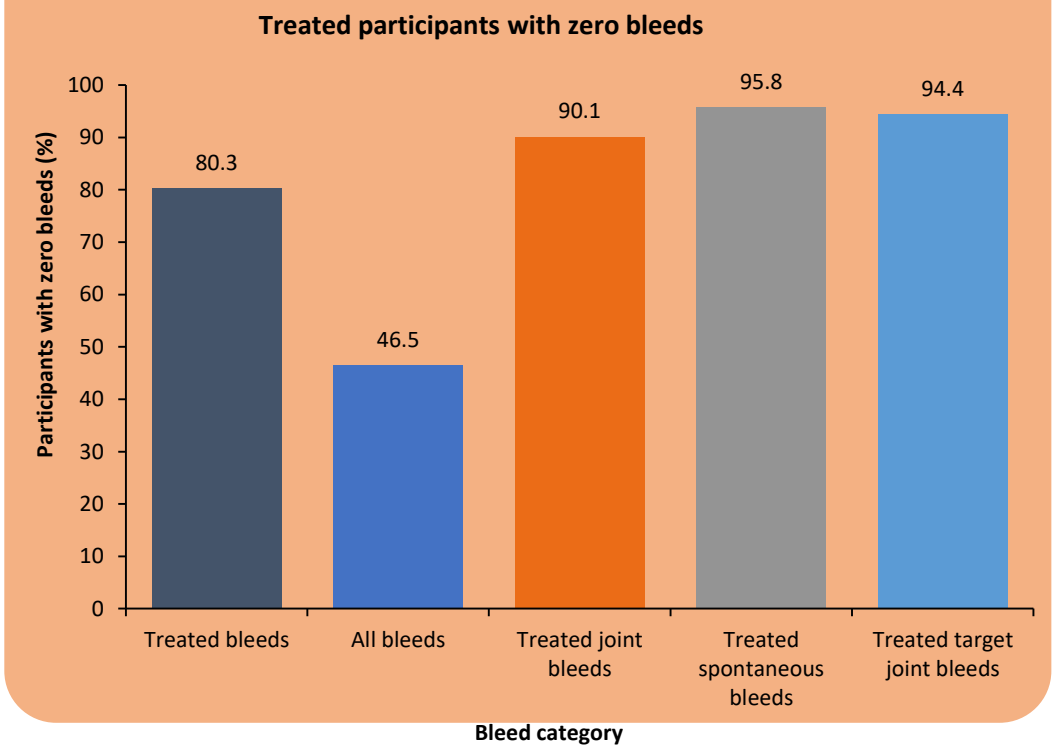
There were no deaths, no thrombotic events or thrombotic microangiopathies, and no treatment withdrawal/modification/interruption

*Grade ≥3 AEs were one case each of concussion and hyperglycaemia in one patient; †the majority of treatment-related AEs were local ISRs; ‡SAEs included one case each of COVID-19, diverticulitis, concussion, contusion, abdominal pain, and hyperglycaemia. One patient had 3 SAEs (one Grade 2 and two Grade 3s); there were no Grade 4 AEs.

AE, adverse event; ISR, injection-site reaction; SAE, serious adverse event.

Emicizumab was efficacious for preventing bleeding events

	Participants (N=72)				
	Treated Bleeds	Treated Joint Bleeds	Treated Spontaneous Bleeds	Treated Target Joint Bleeds	All Bleeds
Model-based ABR (95% CI)	0.9 (0.55–1.52)	0.2 (0.09–0.57)	0.2 (0.11–0.33)	0.1 (0.03–0.40)	2.3 (1.67–3.12)
Calculated mean ABR (95% CI)†	0.9 (0.02–5.48)	0.2 (0.00–4.15)	0.3 (0.00–4.23)	0.1 (0.00–3.92)	2.3 (0.35–7.75)
Calculated median ABR (IQR)†	0.0 (0.00–0.98)	0.0 (0.00–0.00)	0.0 (0.00–0.00)	0.0 (0.00–0.00)	1.0 (0.00–3.11)
Calculated ABR range†	0.00–7.05	0.00–3.63	0.00–6.09	0.00–3.21	0.00–21.04
Participants with zero bleeds, n (%)‡	48 (66.7)	64 (88.9)	59 (81.9)	68 (94.4)	24 (33.3)



- Most median values for bleeding events were **zero**
- All model estimates showed ≤**2.3 bleeds per year**
- ABRs were consistent among moderate and mild subgroups†

- **Less than 10%** of participants reported treated joint bleeds

*Model-based ABR was derived via negative binomial regression; †subgroup analysis for treated bleeds, model-based ABR (95% CI), all treated patients, mild ABR 0.3 (0.10–0.97), moderate ABR 0.9 (0.43–1.89).

ABR, annualised bleeding rate; CI, confidence interval; IQR, interquartile range

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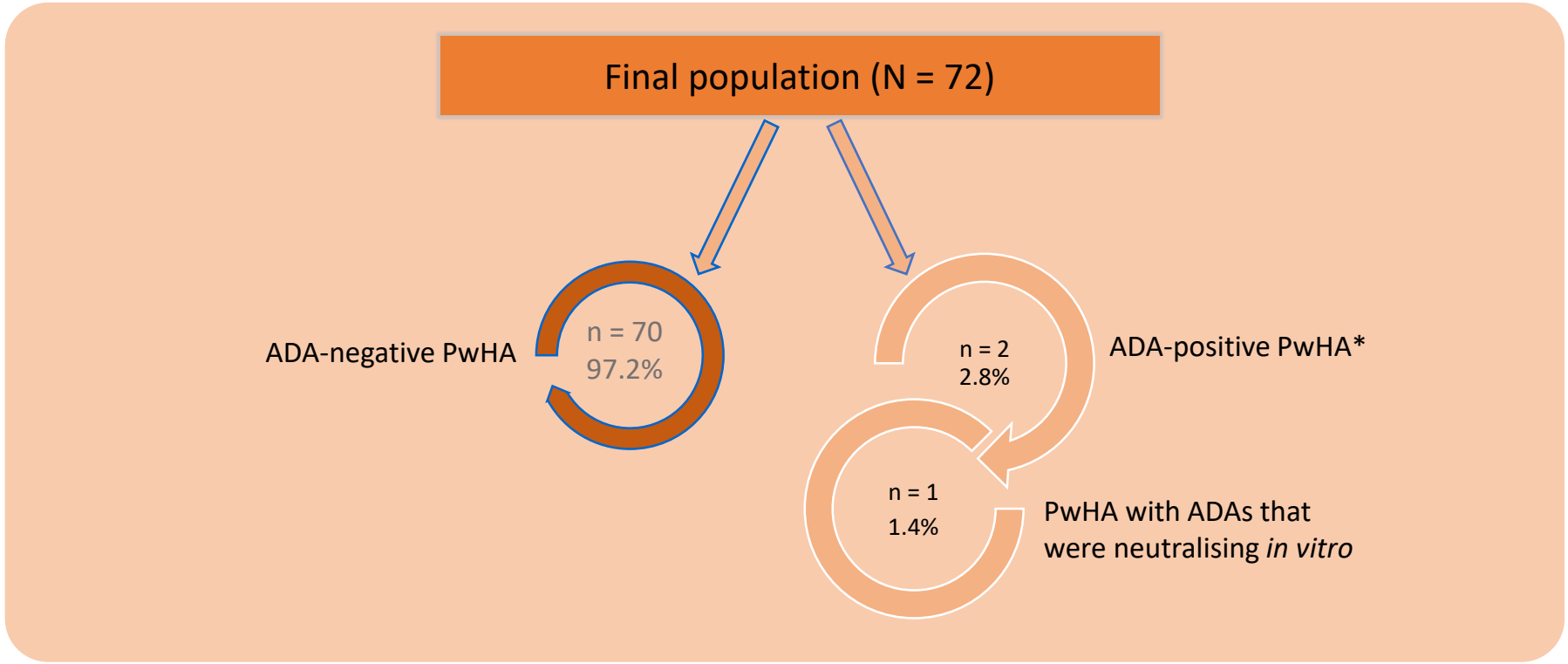
Immunogenicity of emicizumab



ADAs that were neutralising *in vitro* showed no clinical impact, nor impact on emicizumab PK *in vivo*[†]

*The two participants with ADAs both had mild HA, received emicizumab 3 mg/kg Q2W, and had calculated ABRs for all bleeds of zero. ADAs were first detected on Day 85 for both individuals. Neither participant experienced local ISRs or any AE of anaphylaxis;
[†]the participant continued with emicizumab treatment.
ADA, anti-drug antibodies; AE, adverse event; CI, confidence interval; HA, haemophilia A; ISR, injection-site reaction; PK, pharmacokinetics; PwHA, people with haemophilia A; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks

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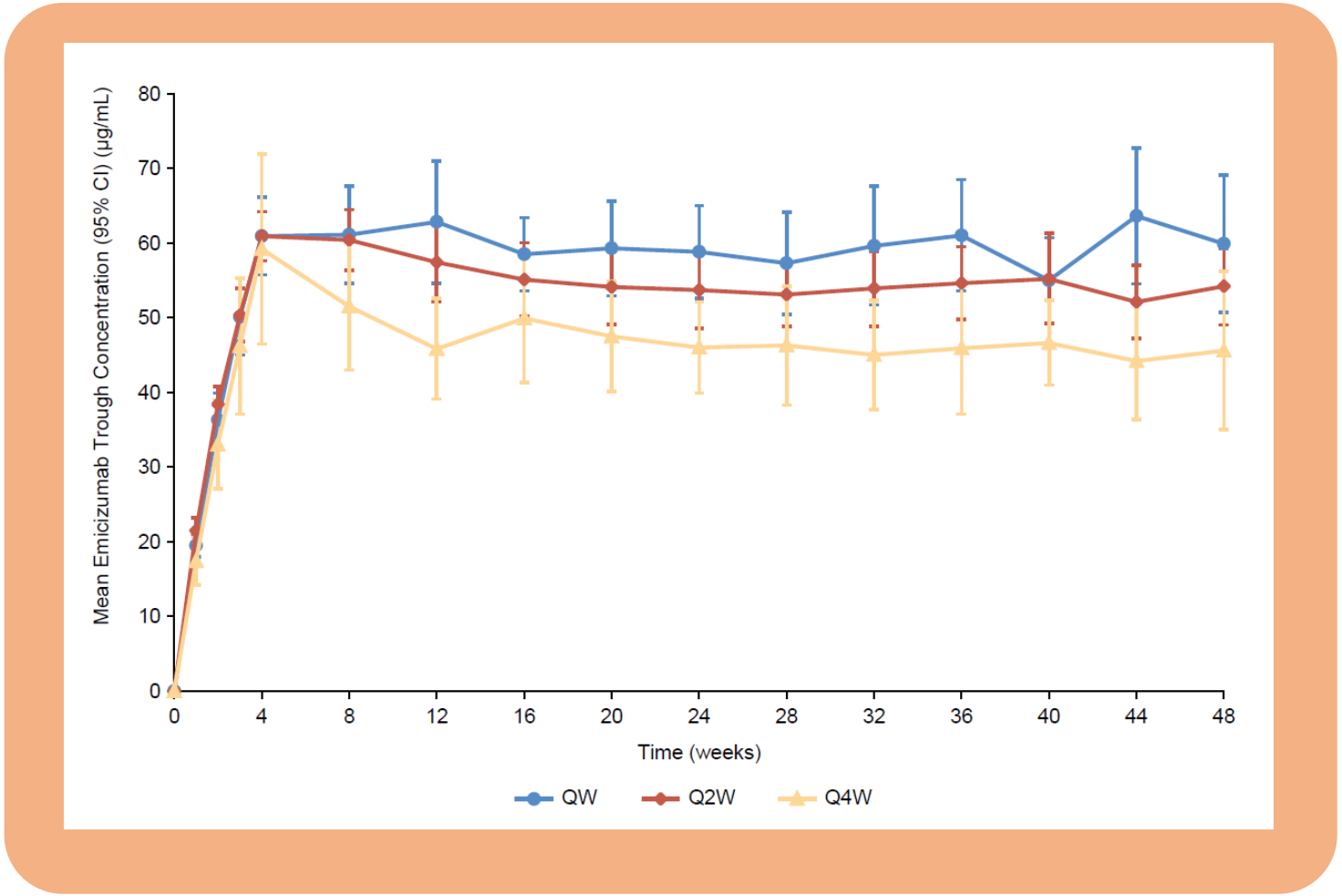
Emicizumab Pharmacokinetics



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Haven 6 summary

In this population of people with moderate or mild HA, no new safety signals were identified and there were no thrombotic events, thrombotic microangiopathies, or deaths.

Efficacy data were consistent across all bleeding endpoints and with other HAVEN studies

Data indicate emicizumab offers a favourable safety profile and an efficacious treatment option for people with moderate/mild HA while reducing treatment burden for those previously receiving either episodic or prophylactic FVIII treatment

Rethinking bleed control : controlled vs uncontrolled vs seemingly controlled

Controlled

- 0 ABR
- Adherent to rigorous prophylaxis regimen
- Current treatment is routine
- May be adapting lifestyle to avoid bleeds

Seemingly Controlled

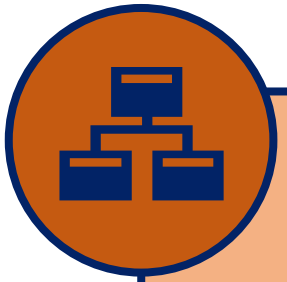
- >0 ABR
- May have accepted a certain level of bleeds as inevitable
- May have modified lifestyle to reduce the number of bleeds
- Current treatment is routine
- May have some joint complications as a consequence of bleeds
- Pain may be an issue

Uncontrolled

- Level of bleeds interferes with daily life
- May be non-adherent to treatment
- Most likely has target joints
- Most likely suffers chronic pain

Optimal care for all haemophilia requires a deliberate shift from disease categorization to phenotypic categorization

Treating according to disease categorization



- Baseline FVIII levels do not always correspond to bleeding phenotype[1]
- Treating according to disease categorization may leave some people with suboptimal bleeding control[1]

F, factor

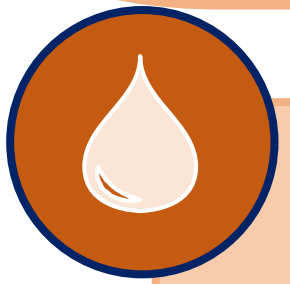
1. Collins PW et al. haemophilia 2021;27(2):192–8.

Optimal care should be based on bleeding phenotype, clinical outcomes, and life goals

Treating according to disease categorization

- Baseline FVIII levels do not always correspond to bleeding phenotype[1]
- Treating according to disease categorization may leave some people with suboptimal bleeding control[1]

Offering prophylaxis according to bleeding phenotype, clinical outcomes, and life goals



- Treatment should be guided by bleeding phenotype and clinical outcomes[2]
- Consideration of individual patient characteristics and life goals can help inform shared decision-making around prophylaxis for all people with hemophilia A[3]

F, factor

1. Collins PW et al. haemophilia 2021;27(2):192–8; 2. Srivastava A et al. haemophilia 2020;26(S6):1–158; 3. Hermans C et al. Blood Rev 2022;52:100890.

Concluding remarks

Replacement therapies have a large number of unmet needs in patients with haemophilia A without inhibitors

Non-replacement therapies have evolved to address the unmet needs.

Haven 6 phase 3 study on emicizumab indicate that it has high efficacy in bleed prevention, and it is safe paediatric, adolescent and adult haemophilia A patients with mild and moderate haemophilia without inhibitors.

Given the similarity in bleeding phenotype between moderate and severe haemophilia, consideration should be given to reclassifying haemophilia by bleeding phenotype rather than clotting factor levels

Thank You!