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Agenda

Welcome
Karl Mahler, Head of Investor Relations

Hemophilia A without inhibitors remains an unmet medical need
Cristin Hubbard, Lifecycle Leader Hemlibra (emicizumab)

HAVEN 3: Phase 3 study of emicizumab prophylaxis in persons with hemophilia A without inhibitors
Johnny Mahlangu, MBBCh, MMed, Haemophilia Comprehensive Care Centre, Faculty of Health Sciences, University of the Witwatersrand and NHLS, Johannesburg, South Africa

HAVEN 4: Phase 3 study of emicizumab prophylaxis given every 4 weeks in persons with hemophilia A with and without inhibitors; additional comments
Gallia Levy, MD, Associate Group Medical Director Hematology

Q&A

Welcome

Karl Mahler
Head of Investor Relations

Hemlibra: Addressing unmet medical needs

Treatment benefit

Improved treatment benefit for patients with and without inhibitors

- Substantially reduced ABR, with zero bleeds in a majority of patients
- Potentially less long-term joint damage and fewer severe / life threatening bleeds
- Prophylactic treatment offers sustained protection
- Non-inhibitor patients did not develop *de novo* FVIII inhibitors

Treatment burden

Reduced treatment burden for patients with and without inhibitors

- Subcutaneous administration
- Less frequent dosing and flexible dosing options (qw, q2w or q4w dosing)
- Less intensive dosing regime

Patient preference

Patients prefer Hemlibra

- Almost all participants in HAVEN 3 and HAVEN 4 preferred Hemlibra over their previous treatment

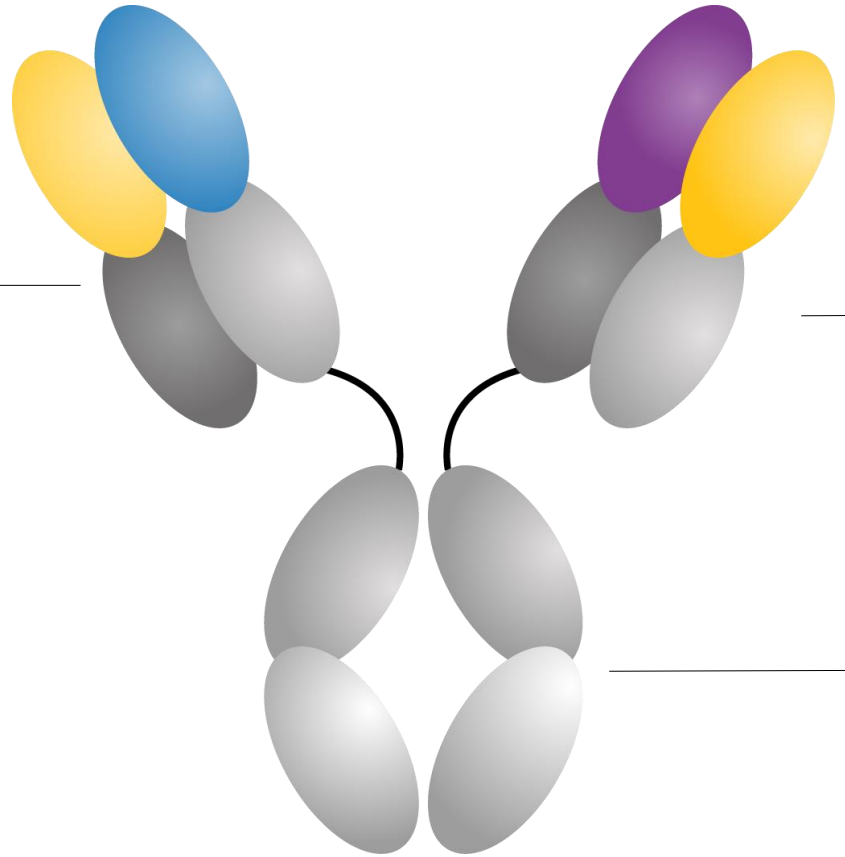
HAVEN 1: Oldenburg et al. ISTH 2017 (data cutoff: 25 Oct 2016); HAVEN 2: Young et al. ASH 2017 (data cutoff: 8 May 2017); HAVEN 3: Mahlangu et al. WFH 2018 (data cutoff: 15 Sep 2017); HAVEN 4: Pipe et al. WFH 2018

Hemlibra (emicizumab) overview

Cristin Hubbard
Lifecycle Leader Hemlibra

Hemlibra: A bispecific monoclonal antibody designed for hemophilia A

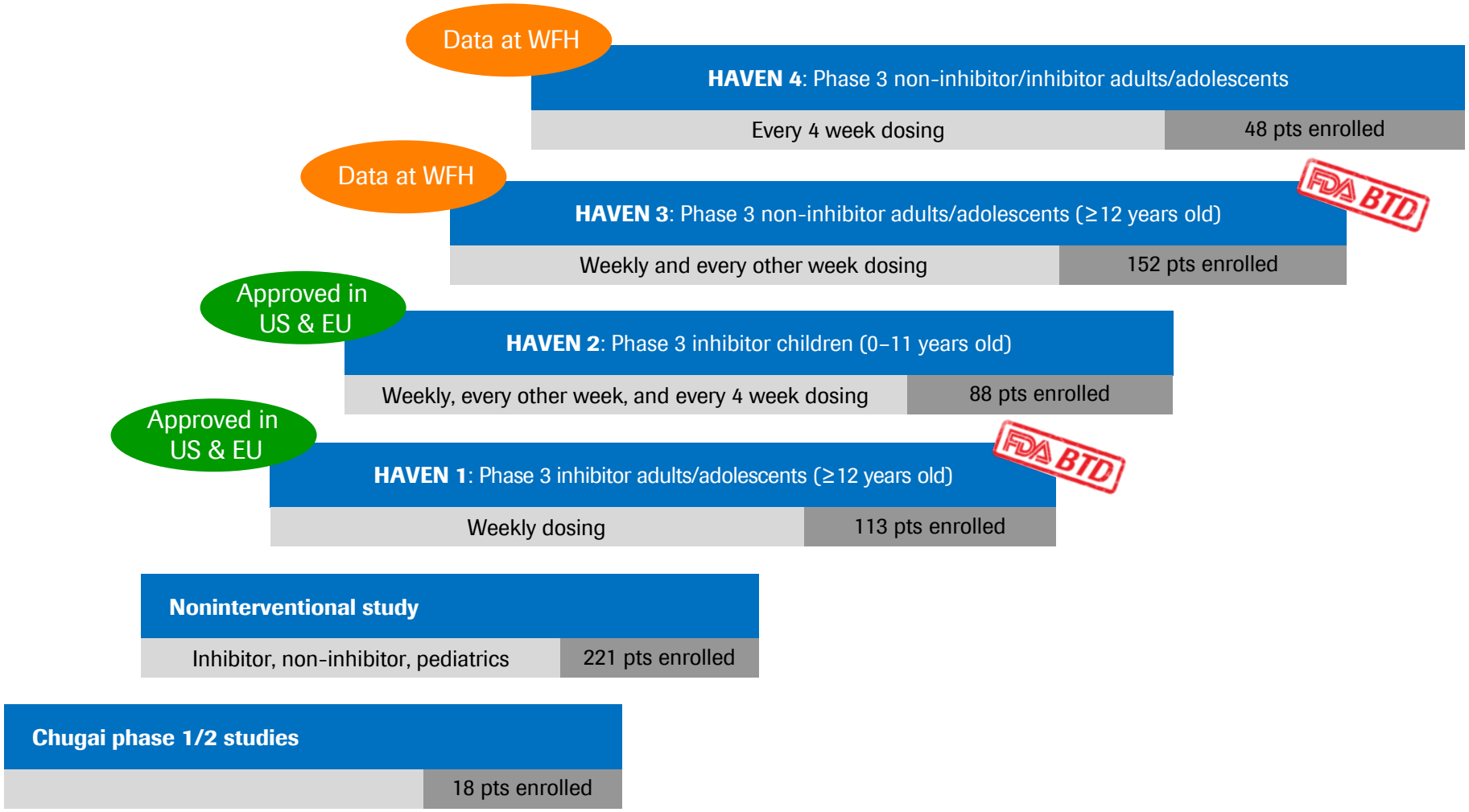
Bridges factors IXa and X, to activate the natural coagulation cascade and restore the blood clotting process



No homology to FVIII

Once weekly subcutaneous injection; less frequent dosing schedules being evaluated

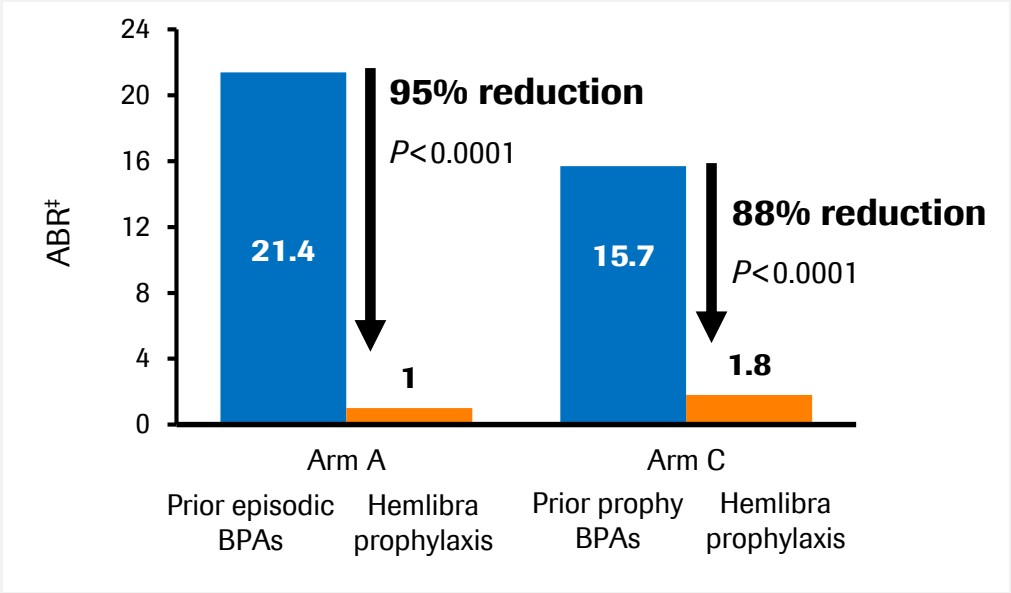
Hemlibra's Ph3 program addresses all people with hemophilia A



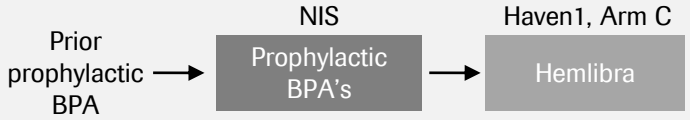
HAVEN 1: Results are statistically robust & clinically meaningful

Primary and all secondary endpoints were met

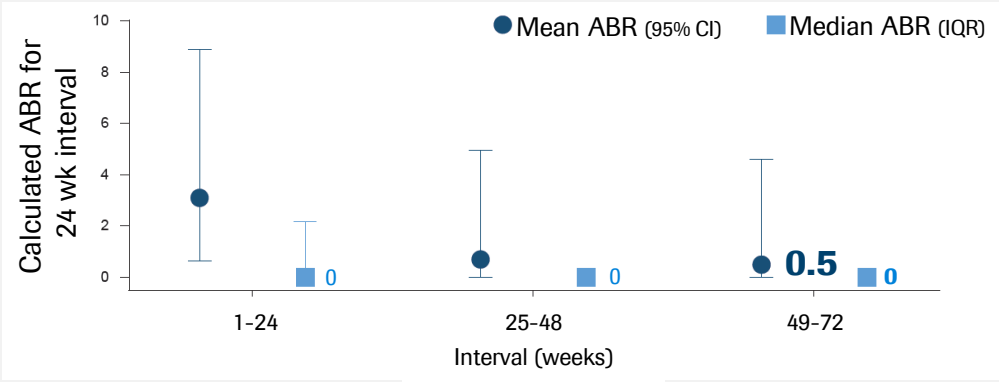
Annualized bleed rate reduction

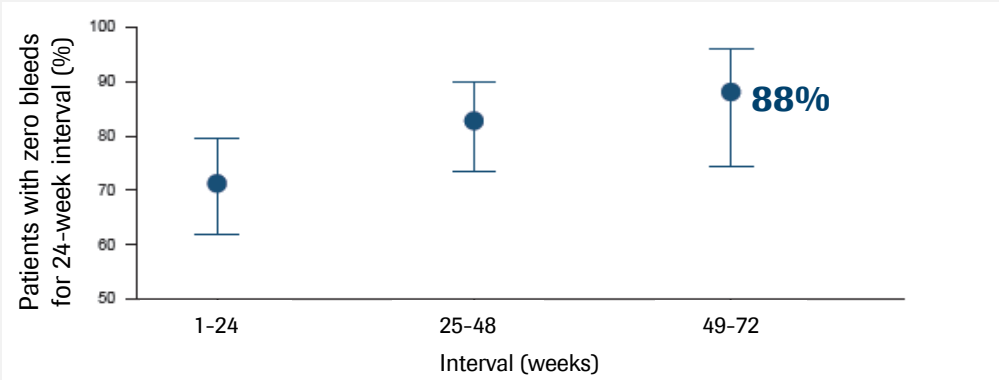


Nearly 10 months additional follow-up



Bleed rates over time





Mancuso et al. ASH 2017

‡ Negative binomial model (Primary analysis data cutoff: Oct 25, 2016; Updated analysis data cutoff: Sep 8, 2017)

ABR=annualized bleeding rate; BPA=bypassing agent; NIS=non-interventional study, IQR=interquartile range

HAVEN 2: Hemlibra prophylaxis prevents or substantially reduces bleeds in pediatric patients with inhibitors

Endpoint	% zero bleeds (95% CI) N=57*	% zero bleeds (95% CI) n=23†	ABR‡ (95% CI) n=23†	Median ABR (IQR) n=23†
Treated bleeds	**94.7** (85.4; 98.9)	**87.0** (66.4; 97.2)	**0.2** (0.06; 0.62)	**0.0** (0.00; 0.00)
All bleeds	**64.9** (51.1; 77.1)	**34.8** (16.4; 57.3)	**2.9** (1.75; 4.94)	**1.5** (0.00; 4.53)
Treated spontaneous bleeds	**98.2** (90.6; 100.0)	**95.7** (78.1; 99.9)	**0.1** (0.01; 0.47)	**0.0** (0.00; 0.00)
Treated joint bleeds	**98.2** (90.6; 100.0)	**95.7** (78.1; 99.9)	**0.1** (0.01; 0.47)	**0.0** (0.00; 0.00)
Treated target joint bleeds	**100** (93.7; 100.0)	**100** (85.2; 100.0)	**Not estimable**	**0.0** (0.00; 0.00)

Most patients reported zero treated bleeds;
Quality of life improvement seen in pediatric patients on Hemlibra prophylaxis

Young et al. ASH 2017

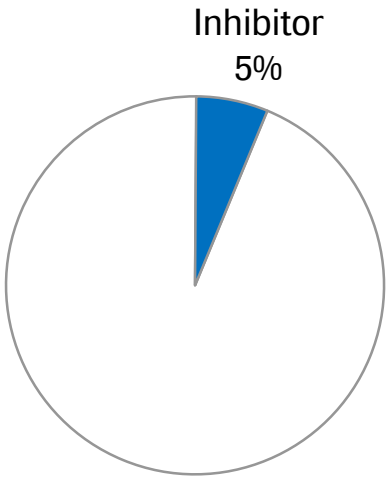
*Aged <12 years; †Primary efficacy results (ABR analysis) based only on patients aged <12 years on study for ≥12 weeks; ‡Negative binomial regression model.
ABR=annualized bleeding rate; BPA=bypassing agent; IQR=interquartile range

Early launch success of Hemlibra in people with inhibitors

25-30% of people with hemophilia A will develop inhibitors to FVIII

Hemophilia A[1]

US: ~22K, EU5: ~25K, RoW: ~121K



Inhibitor

% prophylaxis: **~30%**

Launch update

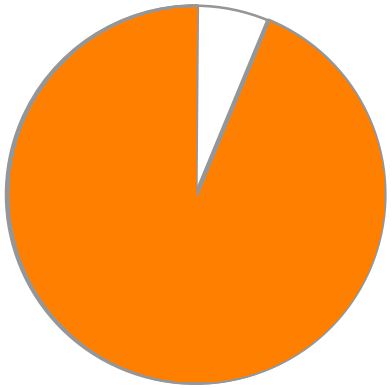
- Hemlibra approved in US (Q4 2017) and EU (Q1 2018)
- US launch demonstrates strong performance driven by patient demand (Q1 2018 US sales of 18.5M CHF); In EU, off to a good start
- CMS has designated Hemlibra as a Part B drug
- In the US, policies with favorable coverage
- Favorable ICER review
- High Hemlibra awareness among inhibitor patients; positive feedback from the community

Prophylaxis[2] On demand

[1]Diagnosed patient prevalence; References: US: CDC UDC 2011, EU5: UKHCDO Annual Report 2016 & Bleeding Disorder Statistics for 2015/2016; Italian Registry of Haemophilia and Allied Disorders. - NATIONAL REGISTRY OF CONGENITAL COAGULOPATHIES. REPORT 2014; J. A. AZNAR et al Haemophilia in Spain; German Haemophilia Registry 2014, FranceCoag online data report, RoW: Estimate according to WFH - "Report on the Annual Global Survey 2016", WFH 2017; [2]Berntorp et al, Haemophilia 2017, CHESS study - O'Hara et al. 2017

Prophylaxis is established as an optimal treatment regimen in the non-inhibitor segment

Hemophilia A[1]
US: ~22K, EU5: ~25K, RoW: ~121K



Non-inhibitor[3]

Severe	Moderate	Mild
~49%	~22%	~29%

% prophylaxis:	~60%	~25%	~10%

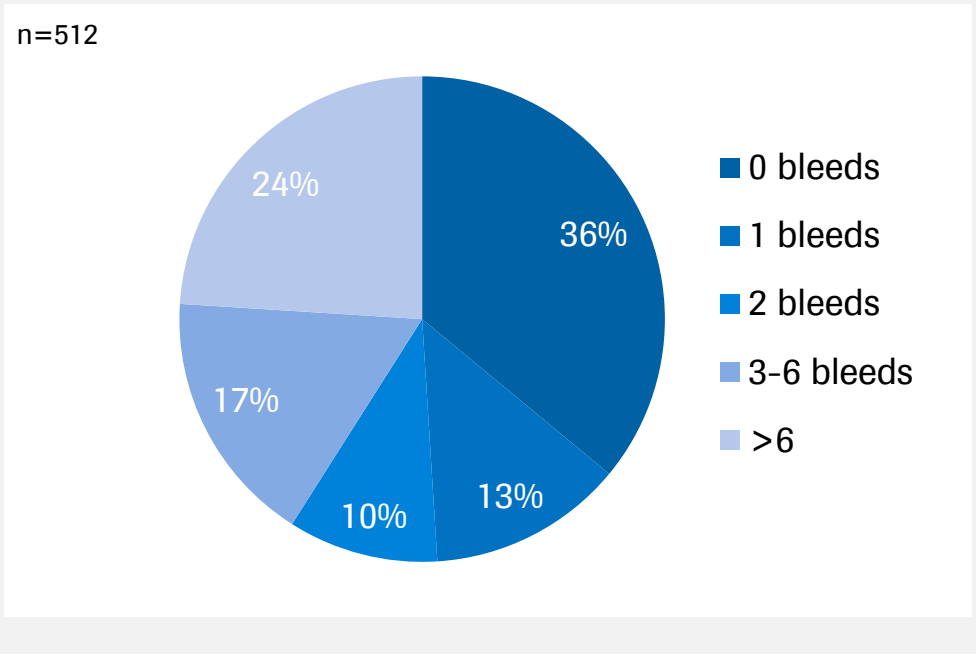
Prophylaxis[2] On demand

Hemlibra could drive uptake of prophylactic treatment

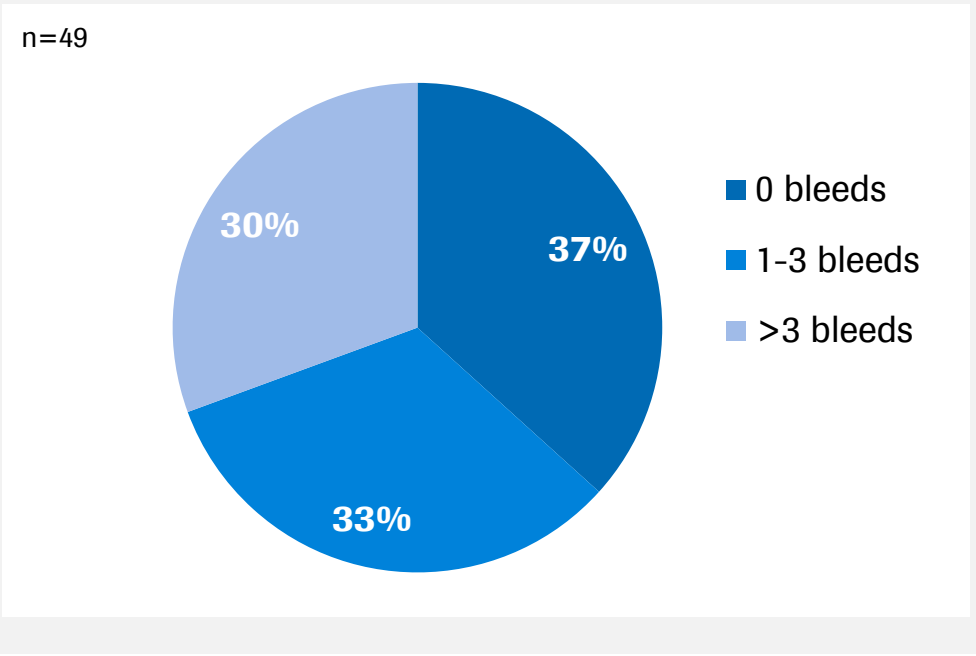
[1]Diagnosed patient prevalence; References: US: CDC UDC 2011, EU5: UKHCDO Annual Report 2016 & Bleeding Disorder Statistics for 2015/2016; Italian Registry of Haemophilia and Allied Disorders. - NATIONAL REGISTRY OF CONGENITAL COAGULOPATHIES. REPORT 2014; J. A. AZNAR et al Haemophilia in Spain; German Haemophilia Registry 2014, FranceCoag online data report, RoW: Estimate according to WFH - "Report on the Annual Global Survey 2016", WFH 2017; [2]Berntorp et al, Haemophilia 2017, CHESS study - O'Hara et al. 2017; [3]Estimate according to WFH - "Report on the Annual Global Survey 2016", WFH 2017

Unmet medical need remains in the non-inhibitor segment despite use of prophylaxis

RWD: Treated bleed category on prophylaxis[1]



NIS (cohort C)*: Treated bleed category on prophylaxis[2]



Potential to improve bleed control and associated disease burden

[1]Oldenburg et al. EAHAD 2017 (Data from the German and International AHEAD study arm, Year 1); [2]Kruse-Jarres R, et al. EAHAD 2018
*NIS Cohort C: adolescent/adult persons with hemophilia A without inhibitors; eligible participants subsequently had the option to enrol in the phase 3 emicizumab HAVEN 3 study (NCT02847637). NIS was conducted between 26 May 2016 and 31 March 2017. ‡Negative binomial regression model; NIS=non-interventional Study; RWD=real world data

HAVEN 3: Phase 3 study of emicizumab prophylaxis in persons with hemophilia A without inhibitors

Johnny Mahlangu, MBBCh, MMed
Haemophilia Comprehensive Care Centre, Faculty of Health Sciences, University of the Witwatersrand and NHLS, Johannesburg, South Africa

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Emicizumab▼ prophylaxis administered once-weekly or every two weeks provides effective bleed prevention in persons with haemophilia A without inhibitors – Results from the phase III HAVEN 3 study

Johnny Mahlangu, **MBBCh, MMed**

Haemophilia Comprehensive Care Centre, Faculty of Health Sciences, University of the Witwatersrand and NHLS, Johannesburg, South Africa

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. These should be reported to the Regulatory authorities in your country according to your national requirements.

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DISCLOSURES FOR:
JOHNNY MAHLANGU

Conflict	Disclosure - if conflict of interest exists
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Speaker Bureau	Alnylam, Bayer, Biotest, Novo Nordisk, Pfizer, Sobi, Shire, WFH
Paid Instructor	No disclosure
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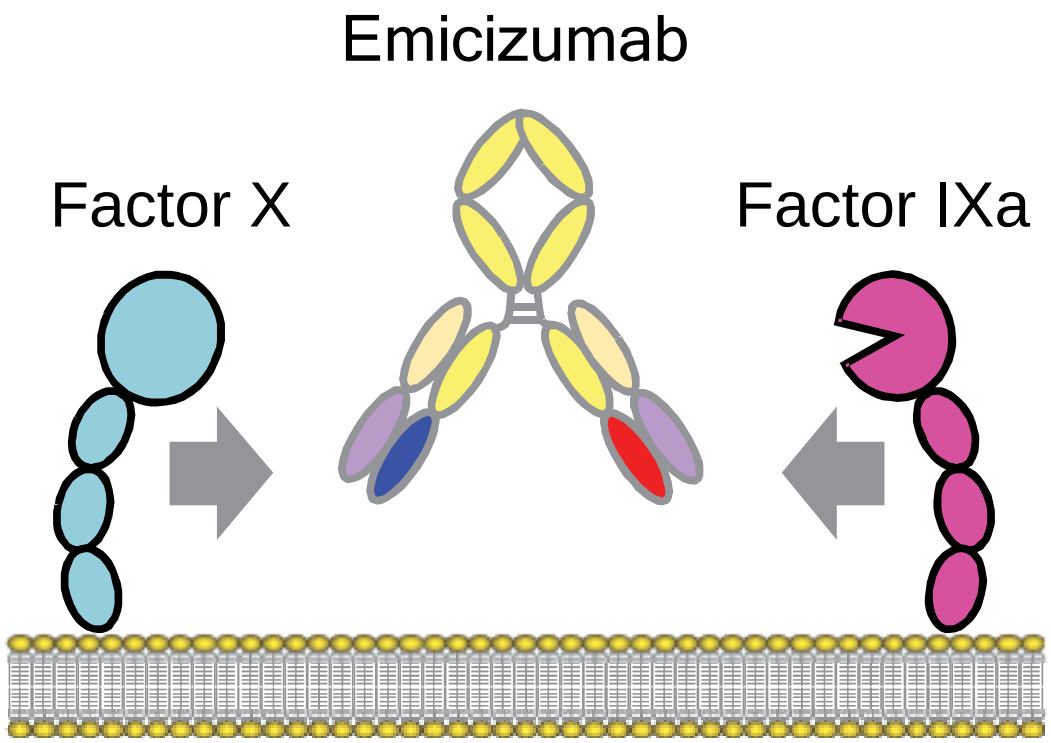
HAVEN 3: Background and objectives

- Regular prophylactic intravenous factor VIII (FVIII) infusions are the optimal treatment approach for severe haemophilia A
  - Clinical and subclinical bleeds may occur despite prophylaxis
  - High treatment burden leading to suboptimal care for those unable to adhere
- Therefore, there's an unmet need for highly effective treatment options with reduced treatment burden
- HAVEN 3 (NCT02847637) was designed to assess the efficacy, safety and pharmacokinetics of subcutaneous emicizumab prophylaxis in persons with haemophilia A without inhibitors

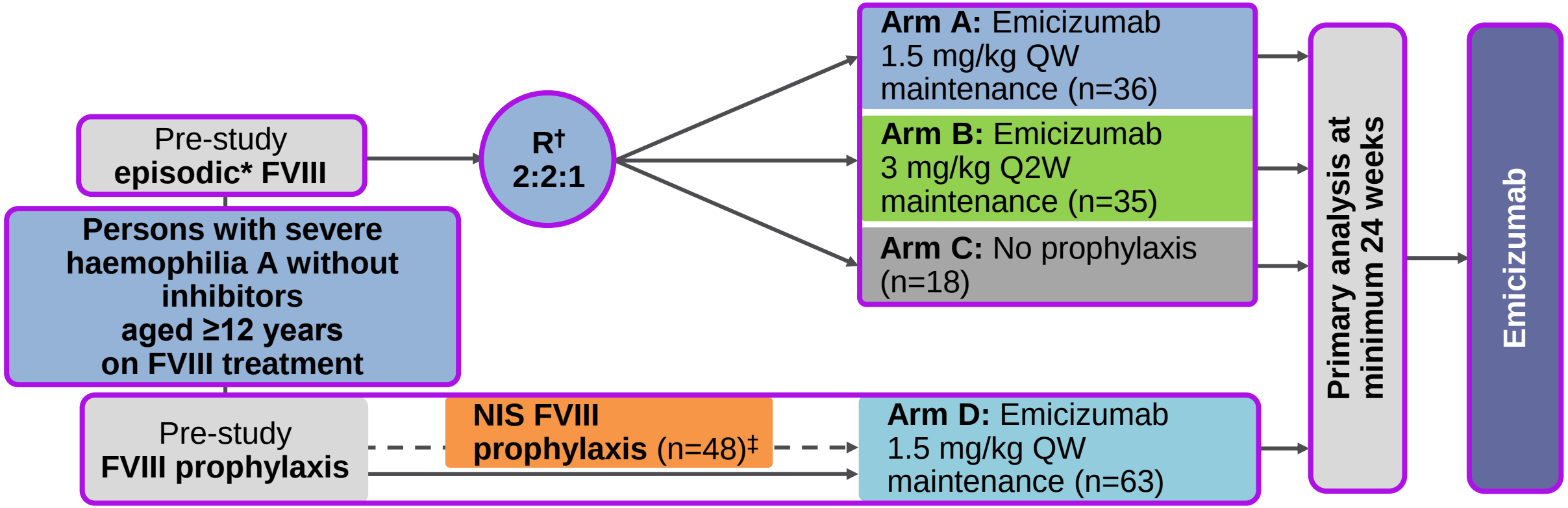
Background: Emicizumab



- Humanised bispecific monoclonal antibody
- Bridges activated FIX (FIXa) and FX to restore function of missing FVIIIa
- No structural homology to FVIII (not expected to induce FVIII inhibitors or be affected by presence of inhibitors)
- Long half-life of ~30 days
- Administered subcutaneously
- Approved in several countries for once-weekly prophylaxis in persons with haemophilia A with inhibitors of all ages

Shima S, et al. *N Engl J Med* 2016;374:2044–53.
Yoneyama K, et al. *Clin Pharmacokinet* 2017 Epub.
HEMLIBRA (emicizumab-kxwh) [prescribing information]. 2017.
HEMLIBRA (emicizumab) [summary of product characteristics]. 2018.
Oldenburg J, et al. *N Engl J Med* 2017; 377(9):809–18.

HAVEN 3: Study design and endpoints



Emicizumab given subcutaneously and all regimens started with a loading series of 3 mg/kg/week for 4 weeks

Primary efficacy	Treated bleed rate (A vs C; B vs C) at minimum 24 weeks
Secondary efficacy	All bleed rate; joint bleed rate; target joint bleed rate; spontaneous bleed rate; HRQoL/health status Bleed rate in prophylaxis Arm D patients vs prior FVIII prophylaxis during NIS
Safety	Includes incidence of ADAs, TEs, FVIII inhibitors

NCT02847637: phase 3, open-label, multicentre, randomised study; initiated 27 Sept 27 2016; data cutoff 15 Sept 15 2017.
*Prior 24-week bleed rate ≥5 for patients receiving episodic FVIII.
†Randomisation stratified based on prior 24-week bleed rate of <9 or ≥9.

ADA, anti-drug antibody; HRQoL, health-related quality of life; QW, once weekly; Q2W, every 2 weeks; R, randomised; TE, thromboembolic event.

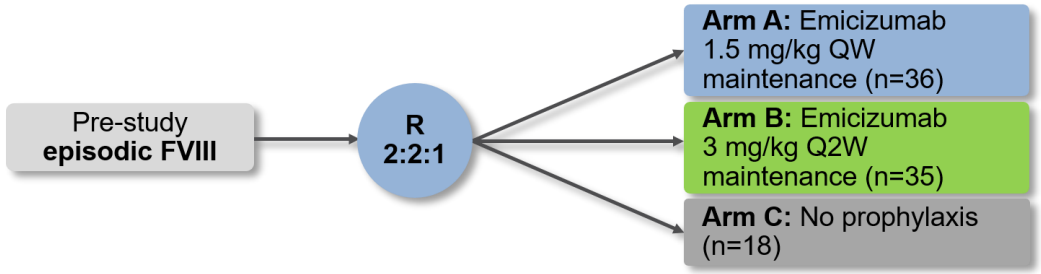
HAVEN 3: Demographics and baseline clinical characteristics

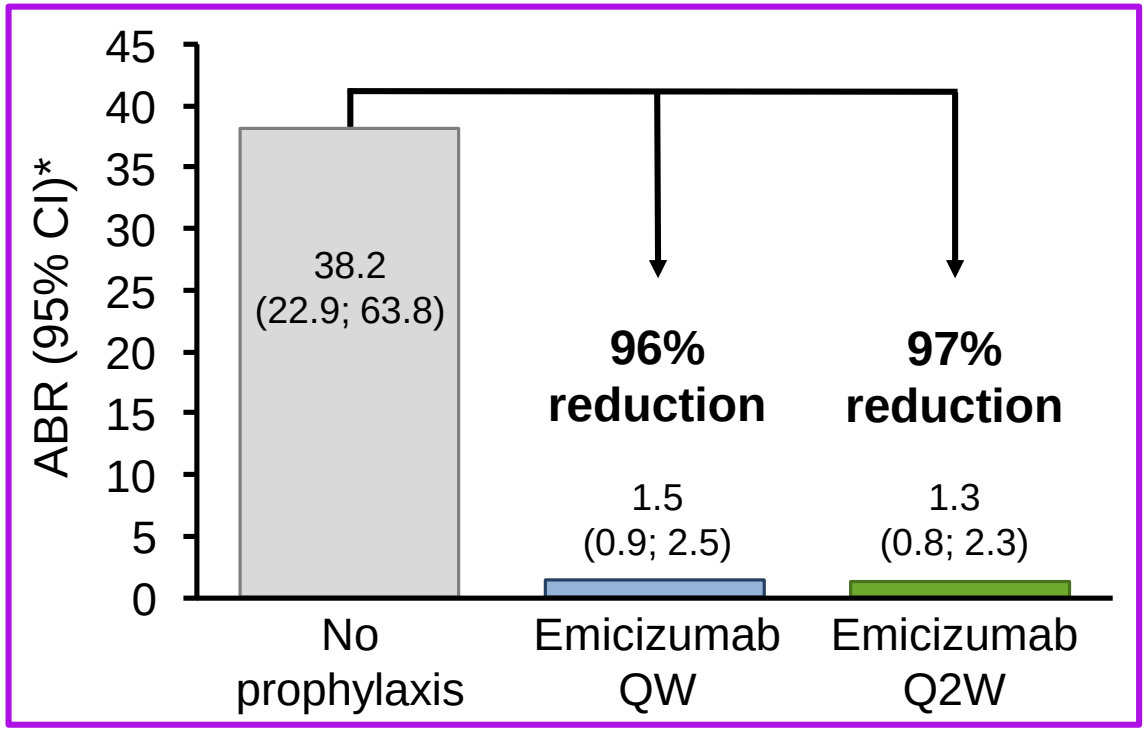
	Prior episodic treatment			Prior prophylaxis	
Characteristic	**Arm A: Emicizumab 1.5 mg/kg QW n=36**	**Arm B: Emicizumab 3 mg/kg Q2W n=35**	**Arm C: No prophylaxis n=18**	**Arm D: Emicizumab 1.5 mg/kg QW n=63**	**Total N=152**
Median (min–max) age, years	36.5 (19–77)	41.0 (20–65)	40.0 (16–57)	36.0 (13–68)	38.0 (13–77)
Age, years, n (%)					
<18	0	0	1 (5.6)	7 (11.1)	8 (5.3)
≥18	36 (100.0)	35 (100.0)	17 (94.4)	56 (88.9)	144 (94.7)
<9 bleeds in 24 weeks before study entry, n (%)	9 (25.0)	5 (14.3)	4 (22.2)	53 (84.1)	71 (46.7)
Target joints, n (%)					
No	2 (5.6)	8 (22.9)	3 (16.7)	37 (58.7)	50 (32.9)
Yes	34 (94.4)	27 (77.1)	15 (83.3)	26 (41.3)	102 (67.1)
>1 target joint	20/34 (58.8)	22/27 (81.5)	14/15 (93.3)	18/26 (69.2)	74/102 (72.5)

HAVEN 3 primary endpoint: Treated bleeds

Emicizumab QW and Q2W significantly reduced ABR vs no prophylaxis

Endpoint	Arm A: Emicizumab 1.5 mg/kg QW n=36	Arm B: Emicizumab 3 mg/kg Q2W n=35	Arm C: No prophylaxis n=18
Median efficacy period, weeks (min–max)	29.6 (17.3–49.6)	31.3 (7.3–50.6)	24.0 (14.4–25.0)
ABR, model based* (95% CI)	1.5 (0.9; 2.5)	1.3 (0.8; 2.3)	38.2 (22.9; 63.8)
Reduction vs Arm C RR, P-value	**96% reduction** 0.04, P<0.0001	**97% reduction** 0.03, P<0.0001	—
Median ABR, calculated (IQR)	0.0 (0.0–2.5)	0.0 (0.0–1.9)	40.4 (25.3–56.7)
Patients with zero bleeds, % (95% CI)	55.6 (38.1; 72.1)	60.0 (42.1; 76.1)	0.0 (0.0; 18.5)
Patients with 0–3 bleeds, % (95% CI)	91.7 (77.5; 98.2)	94.3 (80.8; 99.3)	5.6 (0.1; 27.3)





*ABR calculated with negative binomial regression model.

ABR, annualised bleeding rate; IQR, interquartile range; RR, rate ratio.

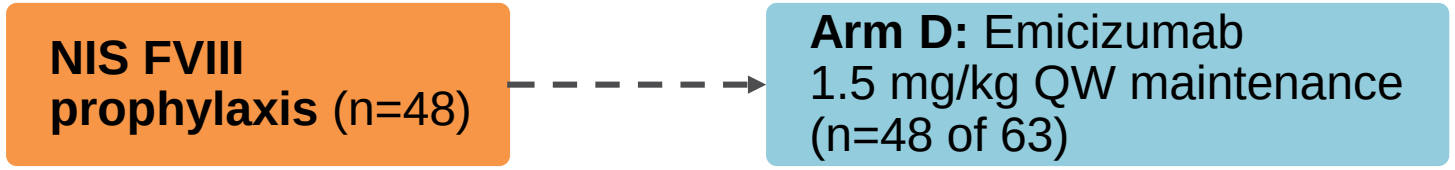
HAVEN 3 bleed-related secondary endpoints

Consistent statistically significant reductions in ABR across endpoints and regimens

Endpoint	Arm A: Emicizumab 1.5 mg/kg QW n=36	Arm B: Emicizumab 3 mg/kg Q2W n=35	Arm C: No prophylaxis n=18
All bleeds			
ABR, model based* (95% CI)	2.5 (1.6; 3.9)	2.6 (1.6; 4.3)	47.6 (28.5; 79.6)
% reduction (RR) vs Arm C, P-value	**95%, P<0.0001**	**94%, P<0.0001**	—
% patients with 0 bleeds (95% CI)	50.0 (32.9; 67.1)	40.0 (23.9; 57.9)	0.0 (0.0; 18.5)
Treated spontaneous bleeds			
ABR, model based* (95% CI)	1.0 (0.5; 1.9)	0.3 (0.1; 0.8)	15.6 (7.6; 31.9)
% reduction (RR) vs Arm C, P-value	**94%, P<0.0001**	**98%, P<0.0001**	—
% patients with 0 bleeds (95% CI)	66.7 (49.0; 81.4)	88.6 (73.3; 96.8)	22.2 (6.4; 47.6)
Treated joint bleeds			
ABR, model based* (95% CI)	1.1 (0.6; 1.9)	0.9 (0.4; 1.7)	26.5 (14.7; 47.8)
% reduction (RR) vs Arm C, P-value	**96%, P<0.0001**	**97%, P<0.0001**	—
% patients with 0 bleeds (95% CI)	58.3 (40.8; 74.5)	74.3 (56.7; 87.5)	0.0 (0.0; 18.5)
Treated target joint bleeds			
ABR, model based* (95% CI)	0.6 (0.3; 1.4)	0.7 (0.3; 1.6)	13.0 (5.2; 32.3)
% reduction (RR) vs Arm C, P-value	**95%, P<0.0001**	**95%, P<0.0001**	—
% patients with 0 bleeds (95% CI)	69.4 (51.9; 83.7)	77.1 (59.9; 89.6)	27.8 (9.7; 53.5)

*ABR calculated with negative binomial regression model.

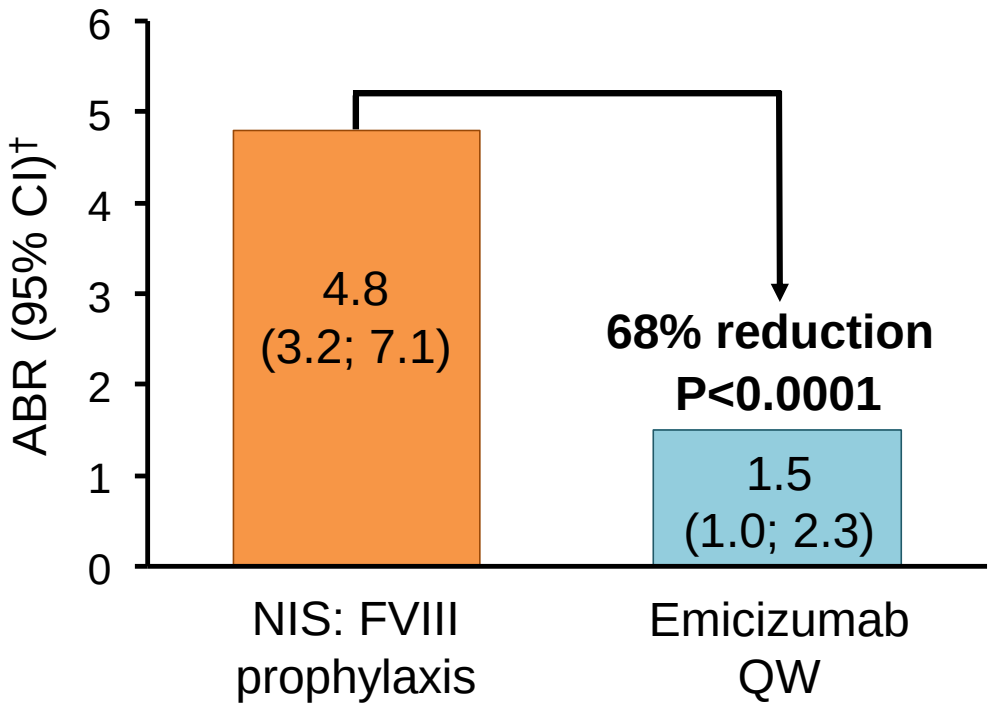
HAVEN 3: Intraindividual comparison methods



- In Arm D (n=63), 48 patients were followed prospectively in the NIS on FVIII prophylaxis and included in an intraindividual analysis
- The NIS prospectively collected data on bleeds and FVIII administration, using the same methodology as in HAVEN 3
- The availability of granular data enabled paired analyses using identical definitions and methodologies
- Investigators attested that each patient received adequate prophylaxis
- Intraindividual comparison controls for interpatient variability (e.g. bleeding characteristics, risk factors for bleeds, and patient recognition of bleeds)

HAVEN 3: Intraindividual comparison of treated bleeds
Emicizumab significantly reduced ABR vs prior FVIII prophylaxis

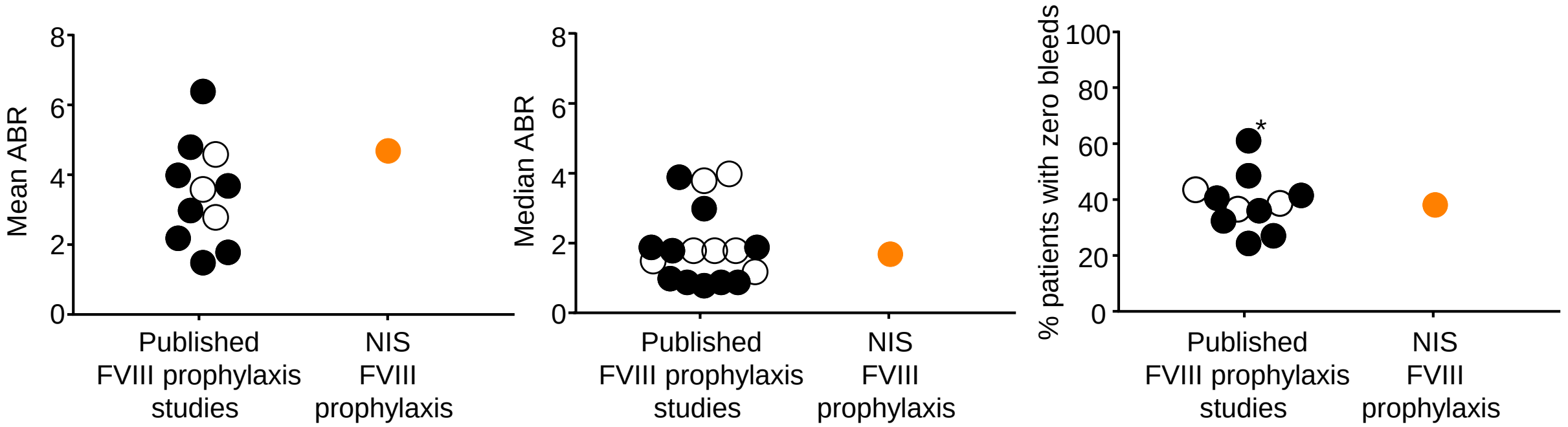
Endpoint	Arm D: Emicizumab 1.5 mg/kg QW n=48*	NIS: FVIII prophylaxis n=48
Duration of efficacy period, median (min-max), weeks	33.7 (20.1–48.6)	30.1 (5.0–45.1)
ABR, model based (95% CI)†	1.5 (1.0; 2.3)	4.8 (3.2; 7.1)
Reduction vs NIS FVIII RR, P-value	**68% reduction** 0.32, P<0.0001	—
Median ABR, calculated (IQR)	0.0 (0.0–2.1)	1.8 (0.0–7.6)
Patients with zero bleeds, % (95% CI)	54.2 (39.2; 68.6)	39.6 (25.8; 54.7)
Patients with 0–3 bleeds, % (95% CI)	91.7 (80.0; 97.7)	72.9 (58.2; 84.7)



- For all patients in Arm D (n=63), ABR (95% CI) was 1.6 (1.1; 2.4) and 55.6% (95% CI, 42.5; 68.1) had zero bleeds

*Data from 48 patients in Arm D who participated in the NIS shown.
†ABR calculated with negative binomial regression model.

FVIII prophylactic therapies: Results of phase 3 studies



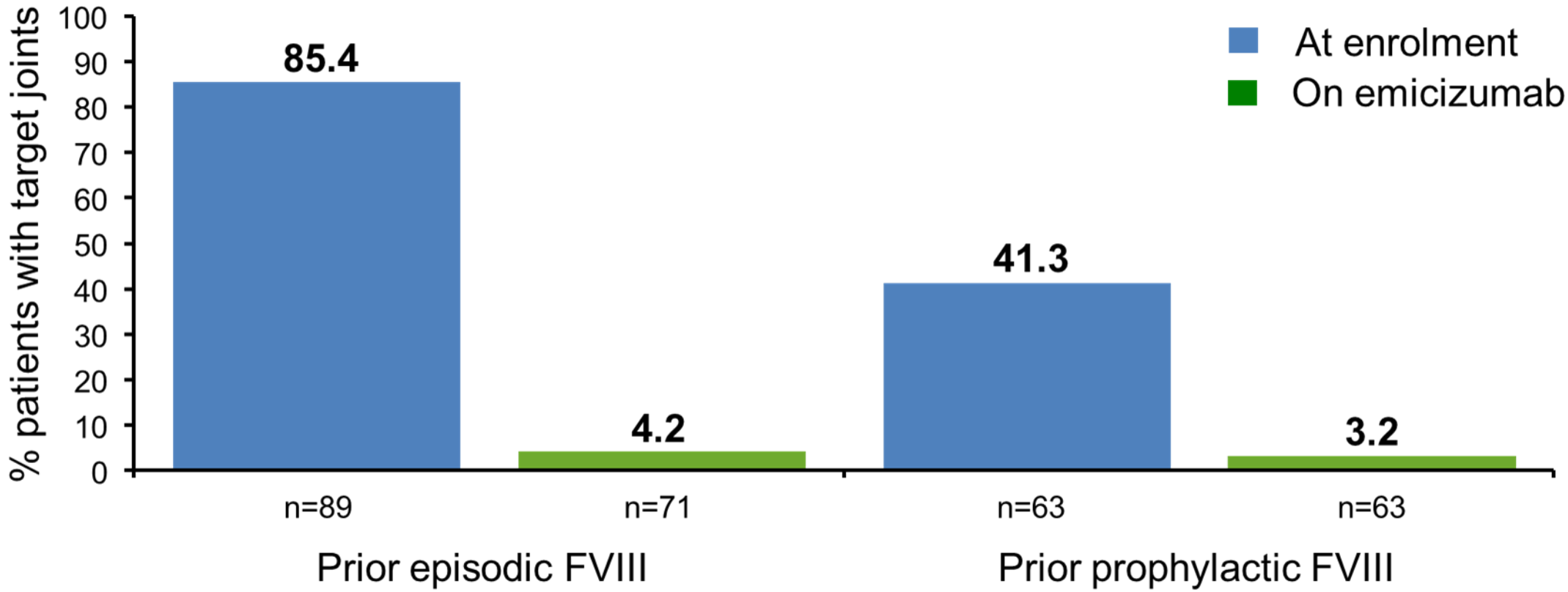
● Published standard half-life FVIII studies[1-5] ○ Published extended half-life FVIII studies[6-9] ● NIS FVIII prophylaxis (n=48)

- Measures for efficacy endpoints not consistently reported across all FVIII studies and some studies included subgroup analyses
  - Advate,[1] NovoEight,[2] Nuwiq,[3] Kovaltry,[4] Afstyla,[5] Eloctate,[6] Adynovate,[7] Bay 94-9027[8] and N8-GP[9]

*Octocog alfa, 3x/week; percentage represents subgroup with observation of 1-year treatment period.

1. Advate USPI; Valentino et al. 2012.
2. NovoEight USPI; Lentz et al. 2013.
3. Nuwiq USPI; Lissitchkov et al. 2015.
4. Kovaltry USPI; Saxena et al. 2016; Kavakli et al. 2015.
5. Afstyla USPI; Mahlangu et al. 2016.
6. Eloctate USPI; Mahlangu et al. 2014.
7. Adynovate USPI; Konkle et al. 2015.
8. Reding et al. 2017.
9. Giangrande et al. 2017.

Proportion of patients with target joints* was reduced with emicizumab



- Incidence of target joints in a post-hoc analysis

*Target joints are defined as a major joint into which ≥3 bleeds occur over a 24-week period. At study entry, the presence of target joints based on bleeds in the 24 weeks before enrolment was recorded. In a post-hoc analysis, target joints were identified within any 24-week period during emicizumab treatment (or the initial period for patients with <24 weeks of treatment) before up-titration (if applicable). Arm C patients after switchover to emicizumab were excluded from this analysis due to the limited follow-up period.

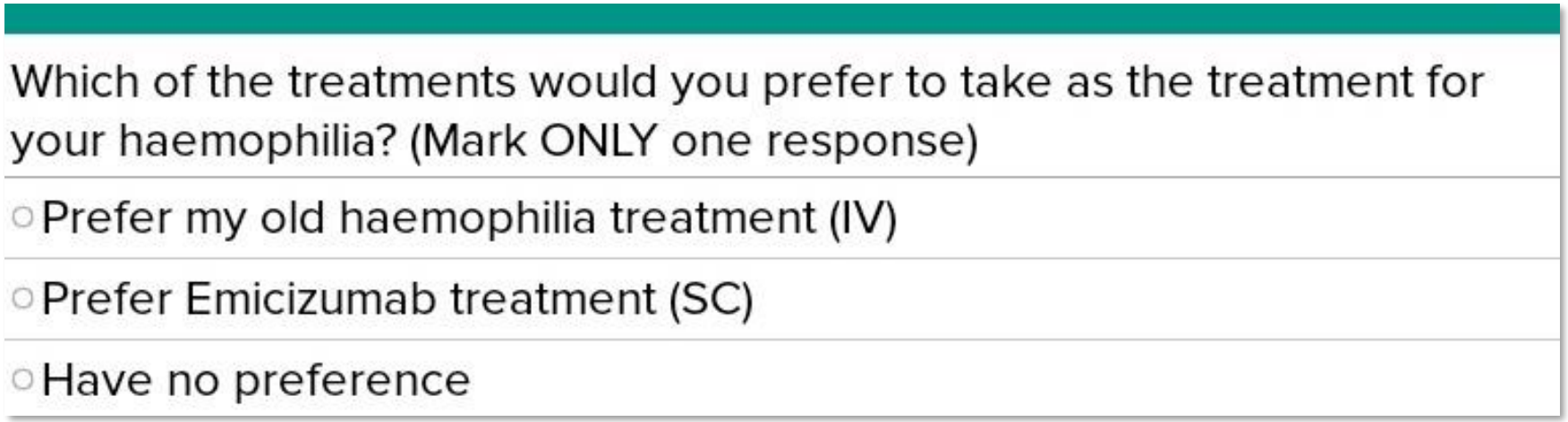
HAVEN 3: Haem-A-QoL Physical Health domain score
Emicizumab resulted in numerical improvement

	Arm A: Emicizumab 1.5 mg/kg QW n=36	Arm B: Emicizumab 3 mg/kg Q2W n=35	Arm C: No prophylaxis n=17*
Physical Health domain score at Week 25			
Patients, n	34	29	13
Adjusted mean difference (95% CI) vs Arm C	12.5 (–2.0; 27.0)	16.0 (1.2; 30.8)	—
P-value	0.089	0.035	—

- Since the comparison of Haem-A-QoL between Arms A and C is not statistically significant, the comparison of Arms B and C is not considered statistically significant due to the order of endpoints in the hierarchical testing framework

*Haem-A-QoL, Haemophilia-Specific Quality of Life Questionnaire for Adults not administered to adolescents (n=1).

HAVEN 3: Patient preference
Nearly all patients preferred emicizumab



- Exploratory efficacy endpoint assessed patient preference using the EmiPref survey
  - Completed by 95/134 (70.9%) eligible patients (Arms A, B and D)
- Of all survey responders, 93.7% (95% CI, 86.8; 97.7) preferred emicizumab
  - Importantly, 45/46 (97.8%) patients in Arm D favoured emicizumab over FVIII prophylaxis

IV, intravenous; SC, subcutaneous.

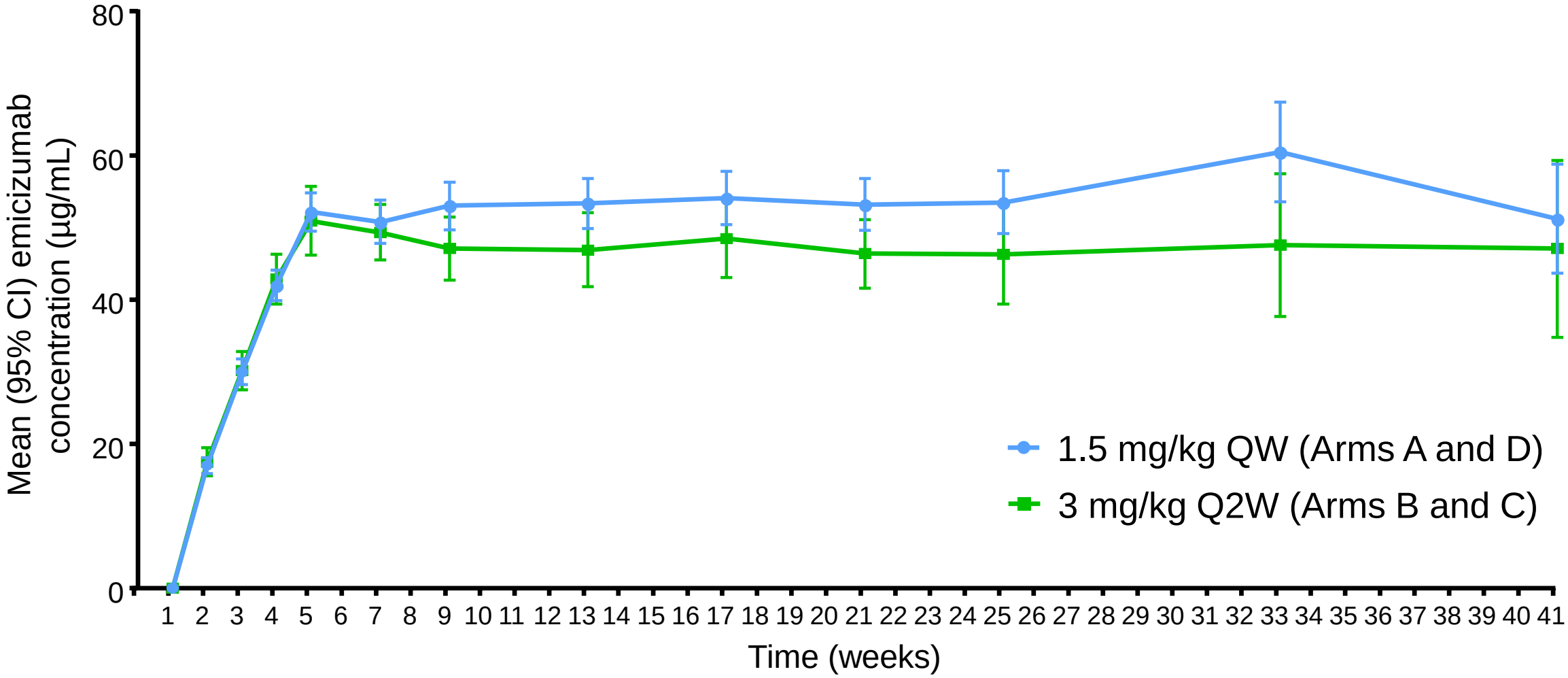
HAVEN 3: Safety summary
Favourable safety profile observed with emicizumab

Event (MedDRA Preferred Term)	Arm A: Emicizumab 1.5 mg/kg QW n=36	Arm B: Emicizumab 3 mg/kg Q2W n=35	Arm C: Emicizumab 3 mg/kg Q2W n=16*	Arm D: Emicizumab 1.5 mg/kg QW n=63	Total N=150
Total number of AEs, n	143	145	19	236	543
Total patients ≥1 AE, n (%)	34 (94.4)	30 (85.7)	8 (50.0)	55 (87.3)	127 (84.7)
Number of serious AEs	1	3	0	10	14
Emicizumab related serious AEs	0	0	0	0	0
Selected AEs occurring in ≥5% of all patients, n (%)†					
Injection-site reaction‡	9 (25.0)	7 (20.0)	2 (12.5)	20 (31.7)	38 (25.3)
Upper respiratory tract infection	4 (11.1)	4 (11.4)	0	8 (12.7)	16 (10.7)
Patients with AE leading to withdrawal, n (%)	0	1 (2.9)	0	0	1 (0.7)

- 1 patient in Arm B discontinued due to multiple mild AEs (insomnia, hair loss, nightmare, lethargy, depressed mood, headache and pruritus); 2 patients were lost to follow-up (Arms A and C, 1 patient each)
- Of 215 events of co-exposure to FVIII and emicizumab in 64 patients, 43 included an average FVIII dose ≥50 IU/kg/24 hours, of which 8 events lasted >24 hours; co-exposure to emicizumab and FVIII was not related to serious AEs, TMA or TEs
- No deaths
- No serious AE was associated with emicizumab per investigator assessment
- No ADAs detected; no patients on emicizumab developed *de novo* FVIII inhibitors

*Data represent period of emicizumab prophylaxis only; at the clinical cutoff date, 1 patient was lost to follow-up and another was waiting to start emicizumab.
†Other AEs in ≥5% of all patients: arthralgia (19%), nasopharyngitis (12%), headache (11%), and influenza (6%).
‡Grades 1–2 AE. 1 additional patient in Arm D (and total column) reported an “injection site erythema” not “injection site reaction” as the Preferred Term.
AE, adverse event; TMA, thrombotic microangiopathy.

HAVEN 3: Emicizumab pharmacokinetics
QW or Q2W achieve sustained effective trough concentrations



- Emicizumab trough concentrations were consistent with a T ½ of ~30 days

Arm C data represents patients who switched to emicizumab prophylaxis after completing ≥24 weeks on study.

Yoneyama K, et al. *Clin Pharmacokinet* 2017 Epub.

HAVEN 3: Conclusions

- Emicizumab prophylaxis QW or Q2W achieved highly effective prophylaxis of bleeds in adults/adolescents with haemophilia A without inhibitors
- Notably, an intraindividual comparison demonstrated superiority of bleed rate with emicizumab (QW) over prior FVIII prophylaxis
- Nearly all patients preferred emicizumab over their prior haemophilia treatment
- A favourable safety profile for emicizumab was observed in HAVEN 3
  - No TE or TMA, and no unexpected safety signal
  - No related serious AEs
  - No ADAs or *de novo* FVIII inhibitors detected
- Subcutaneous emicizumab prophylaxis can provide a highly efficacious and flexible treatment option, with reduced burden for persons with haemophilia A

Co-authors

- Johannes Oldenburg: Universitätsklinikum Bonn, Bonn, Germany
- Ido Paz-Priel: Genentech Inc., South San Francisco, CA, USA
- Claude Negrier: Louis Pradel University Hospital, Lyon, France
- Markus Niggli: F. Hoffmann-La Roche Ltd., Basel, Switzerland
- Maria Elisa Mancuso: Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy
- Christophe Schmitt: F. Hoffmann-La Roche Ltd., Basel, Switzerland
- Victor Jiménez-Yuste: Hospital Universitario La Paz, Autónoma University, Madrid, Spain
- Christine Kempton: Department of Hematology and Medical Oncology, HoG Inc., Emory School of Medicine, Atlanta, GA, USA
- Christophe Dhalluin: F. Hoffmann-La Roche Ltd., Basel, Switzerland
- Michael Callaghan: Children's Hospital of Michigan, Detroit, MI, USA
- Willem Bujan: Instituto Costarricense de Investigaciones Científicas, San José, Costa Rica
- Midori Shima: Department of Pediatrics, Nara Medical University, Kashihara, Japan
- Joanne I. Adamkewicz: Genentech Inc., South San Francisco, CA, USA
- Elina Asikanius: F. Hoffmann-La Roche Ltd., Basel, Switzerland
- Gallia G. Levy: Genentech Inc., South San Francisco, CA, USA
- Rebecca Kruse-Jarres: Washington Center for Bleeding Disorders at Bloodworks Northwest, Seattle, WA, USA

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HAVEN 4: Phase 3 study of emicizumab prophylaxis given every 4 weeks in persons with hemophilia A with and without inhibitors; additional comments

Gallia Levy, MD, PhD
Global Development Leader Hemlibra

HAVEN 4: Phase 3 study of emicizumab prophylaxis given every 4 weeks in persons with hemophilia A with and without inhibitors

Additional comments

WFH 2018 WORLD CONGRESS

Emicizumab▼subcutaneous dosing every 4 weeks is safe and efficacious in the control of bleeding in persons with haemophilia A with and without inhibitors – Results from the phase 3 HAVEN 4 study

Steven Pipe, MD

University of Michigan, C.S. Mott Children's Hospital, Ann Arbor, MI, USA

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. These should be reported to the Regulatory authorities in your country according to your national requirements.

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WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
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DISCLOSURES FOR:
STEVEN PIPE

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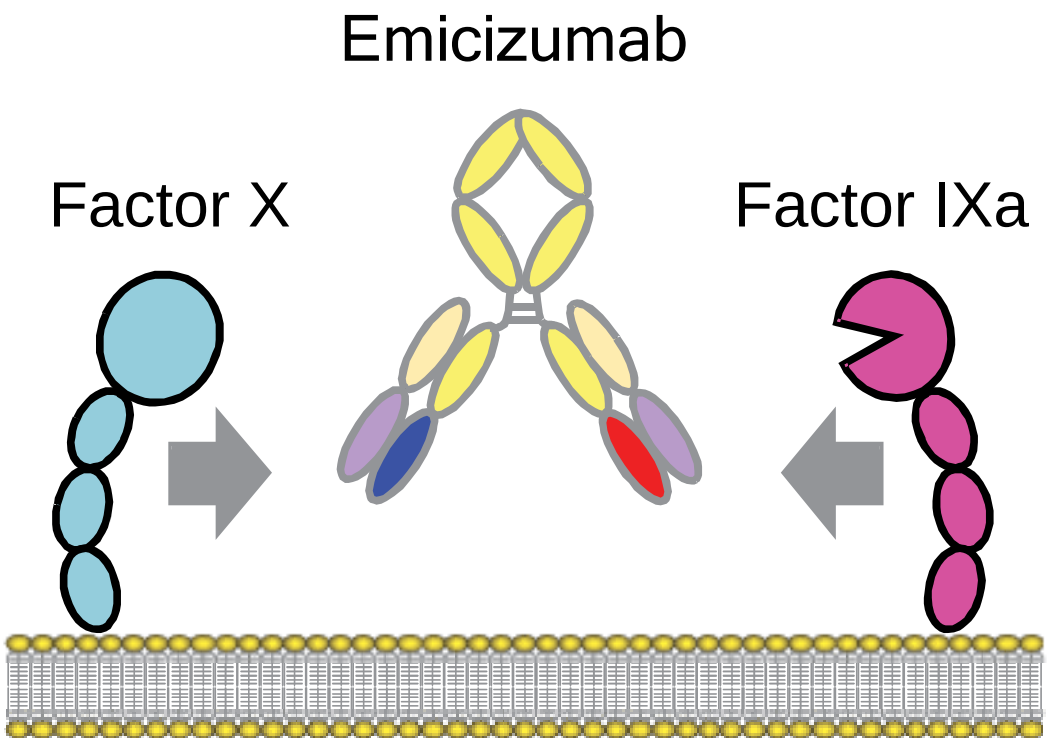
Director, Officer, Employee	MASAC-NHF
Shareholder	No disclosure
Honoraria	No disclosure
Advisory Committee	No disclosure
Consultant	Alnylam, ApcinteX, Bayer, BioMarin, Bioverativ, CSL Behring, F. Hoffmann La-Roche, Novo Nordisk, Pfizer, Shire, uniQure

Background: Emicizumab



- Humanised bispecific monoclonal antibody
- Bridges activated factor IX (FIXa) and FX to restore function of missing FVIIIa
- No structural homology to FVIII (not expected to induce FVIII inhibitors or be affected by presence of FVIII inhibitors)
- Long half-life of ~30 days
- Administered subcutaneously
- Approved in several countries for once-weekly prophylaxis in persons with haemophilia A with inhibitors of all ages

Shima S, et al. *N Engl J Med* 2016;374:2044–53.
Yoneyama K, et al. *Clin Pharmacokinet* 2017 Epub.
HEMLIBRA (emicizumab-kxwh) [prescribing information]. 2017.
HEMLIBRA (emicizumab) [summary of product characteristics]. 2018.
Oldenburg J, et al. *N Engl J Med* 2017; 377(9):809–18.

Emicizumab clinical trials

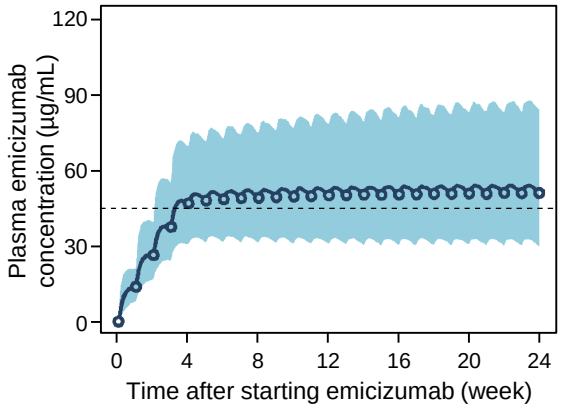
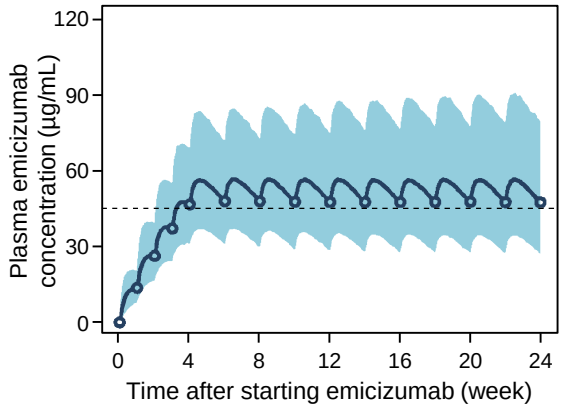
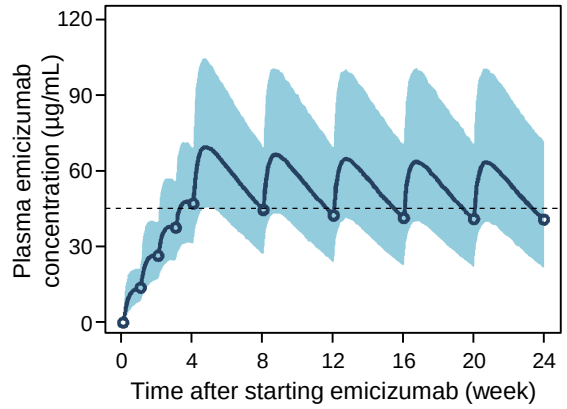
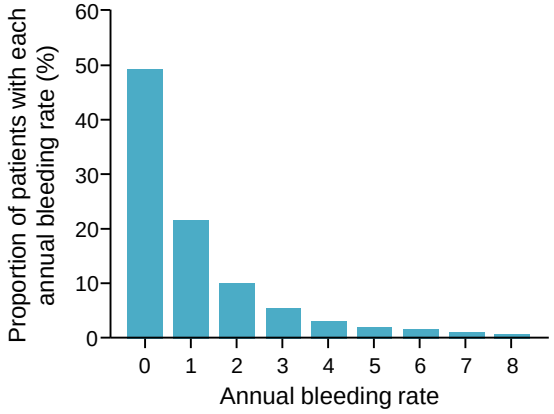
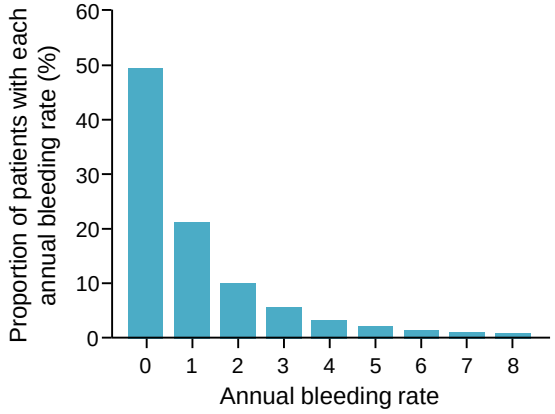
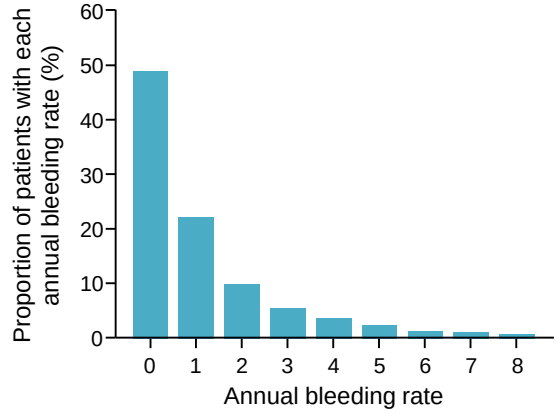
Clinical trial	Population	ABR, treated bleeds: emicizumab prophylaxis vs no prophylaxis	% patients with zero treated bleeds	ABR, treated bleeds: emicizumab prophylaxis vs prior prophylaxis in NIS
HAVEN 1 (NCT02622321)	PwHA ≥12 years with FVIII inhibitors	▪ 87% reduction (QW)*	▪ 63% (QW), 6% (no prophylaxis)	▪ 79% reduction with emicizumab QW vs prior BPA prophylaxis
HAVEN 2 (NCT02795767)	PwHA <12 years with FVIII inhibitors	▪ N/A (no comparator)	▪ 87% (QW)	▪ 99% reduction with emicizumab QW vs prior BPA prophylaxis
HAVEN 3 (NCT02847637)	PwHA ≥12 years without FVIII inhibitors	▪ 96% reduction (QW) ▪ 97% reduction (Q2W)	▪ 56% (QW), 60% (Q2W), 0% (no prophylaxis)	▪ 68% reduction with emicizumab QW vs prior FVIII prophylaxis
HAVEN 4 (NCT03020160)	**PwHA ≥12 years with or without FVIII inhibitors**	▪ **Primary analyses evaluating emicizumab Q4W prophylaxis on bleeding rate, safety, PK**		

*Improved bleeding rate observed in subsequent 24-week periods beyond initial 24-weeks.

Oldenburg J, et al. *N Engl J Med* 2017;377:809–18.
Mancucso, ME, et al. *Blood* 2017;130:1071.
Young G, et al. *Blood* 2017;130:85.
Genentech Press Release. Nov 19, 2017.
Mahlangu J, et al. Presented at WFH 2018. Abstract 854.

ABR, annualized bleeding rate; BPA, bypassing agent; PwHA, persons with Haemophilia A; PK, pharmacokinetics; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, once weekly.

PK and efficacy modelling for different emicizumab dosing regimens

	1.5 mg/kg QW	3 mg/kg Q2W	6 mg/kg Q4W
PK modelling			
Modelled ABR			

- All 3 regimens were expected to achieve clinically efficacious concentrations and provide similar efficacy
- All dosing regimens begin with loading period of 3 mg/kg/week for 4 weeks, followed by maintenance dose as indicated

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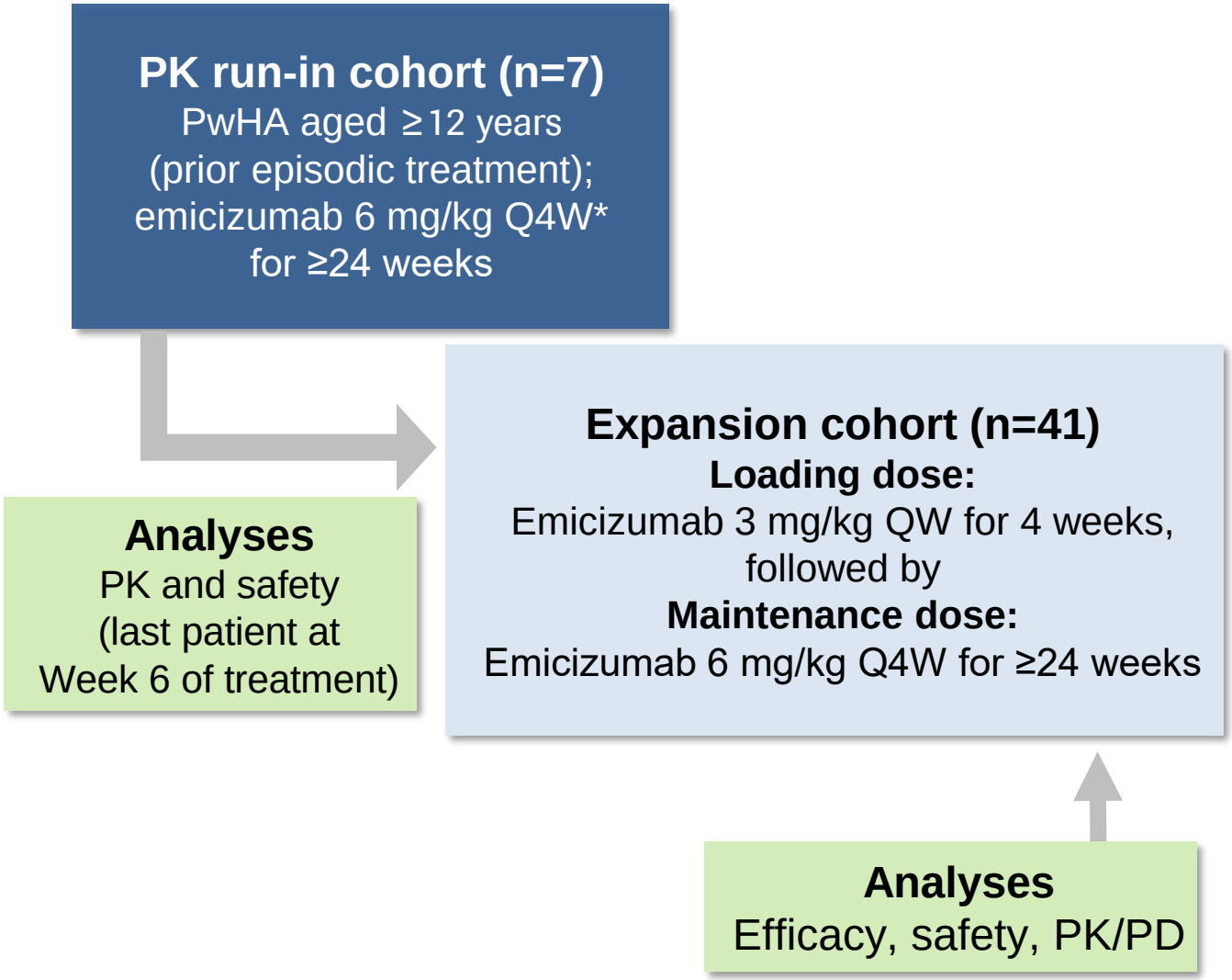
HAVEN 4: Study design



- Expansion cohort:
  - Severe haemophilia A with or without inhibitors
  - Documented episodic or prophylactic treatment with FVIII replacement or BPAs for ≥24 weeks before study entry
  - Median (range) efficacy period: 25.6 (24.1–29.4) weeks

NCT03020160: phase 3, open-label, multicentre, randomised study. Data cutoff: 15 December 2017.
*Dosing regimens different in PK run-in and expansion cohorts.

PD, pharmacodynamics; Q4W, every 4 weeks.

HAVEN 4
Expansion cohort: Study objectives

- Efficacy
  - Treated bleed rate, all bleed rate, joint bleed rate, target joint bleed rate, spontaneous bleed rate
  - Health-related quality of life/health status and functional outcomes (e.g. absences), preference (EmiPref)
- Safety
  - Incidence and severity of AEs, including thromboembolic events, severe hypersensitivity, injection-site reactions and laboratory abnormalities
  - Drug discontinuation
  - Incidence of ADAs and *de novo* FVIII inhibitors (in PwHA without inhibitors)
- Pharmacokinetic
  - Characterization of the PK profile after multiple Q4W subcutaneous doses of 6 mg/kg emicizumab
- Exploratory
  - Biomarkers (e.g. aPTT, thrombin generation assay, FVIII activity)

ADA, anti-drug antibodies, AE, adverse event; aPTT, activated partial thromboplastin time.

HAVEN 4
Demographics and baseline characteristics

Characteristic	Emicizumab 6 mg/kg Q4W N=41
Male, n (%)	41 (100.0)
Age	
Median (min–max), years	39 (14–68)
≥18 years, n (%)	38 (92.7)
Severe haemophilia A, n (%)*	40 (97.6)
Bleeds in 24 weeks before study entry, n (%)	
<9	28 (68.3)
≥9	13 (31.7)
Target joints, n (%)	
No	16 (39.0)
Yes	25 (61.0)
FVIII inhibitor present at study entry, n (%)	5 (12.2)

Data cutoff: 15 Dec 2017.
*Includes 1 patient with mild haemophilia and inhibitors (32 BU/mL), and <1% FVIII activity at study entry.

HAVEN 4
Effective bleed control achieved with emicizumab Q4W

- Median (range) efficacy period, 25.6 (24.1–29.4) weeks
- Majority (38/51 [74.5%]) of treated bleeds were traumatic

Bleeds n=41 pts	ABR, model based (95% CI)*	Median ABR, calculated (IQR)	Zero bleeds, % pts (95% CI)	0–3 bleeds, % pts (95% CI)
Treated bleeds	2.4 (1.4; 4.3)	0.0 (0.0; 2.1)	56.1 (39.7; 71.5)	90.2 (76.9; 97.3)
All bleeds	4.5 (3.1; 6.6)	2.1 (0.0; 5.9)	29.3 (16.1; 45.5)	80.5 (65.1; 91.2)
Treated spontaneous bleeds	0.6 (0.3; 1.5)	0.0 (0.0; 0.0)	82.9 (67.9; 92.8)	97.6 (87.1; 99.9)
Treated joint bleeds	1.7 (0.8; 3.7)	0.0 (0.0; 1.9)	70.7 (54.5; 83.9)	95.1 (83.5; 99.4)
Treated target joint bleeds	1.0 (0.3; 3.3)	0.0 (0.0; 0.0)	85.4 (70.8; 94.4)	97.6 (87.1; 99.9)

Data cutoff: 15 Dec 2017.
*ABR calculated with negative binomial regression model.

IQR, interquartile range; pt, patient.

HAVEN 4 Haem-A-QoL Physical Health domain score
Emicizumab resulted in a numerical improvement

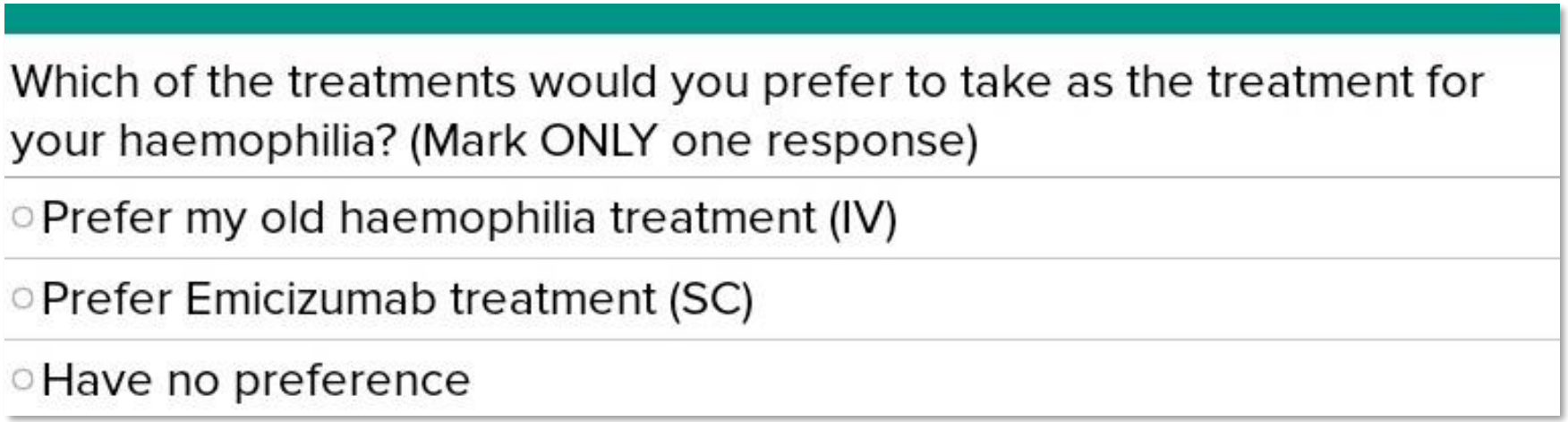
	Emicizumab 6 mg/kg Q4W N=38*	
	Baseline	**Week 25**
Patients, n	38	37
Physical Health domain score, mean (SD)	47.0 (25.1)	32.4 (25.4)
Change from baseline, mean (95% CI)	–	–15.1 (–22.4; –7.8)

- Change from baseline in the Physical Health domain score for meaningful improvements: ≥10 points (responder threshold)

*Haem-A-QoL, Haemophilia-Specific Quality of Life Questionnaire for Adults not administered to adolescents (n=3).

Wyrwich KW, et al. *Haemophilia* 2015: 21; 578–584.

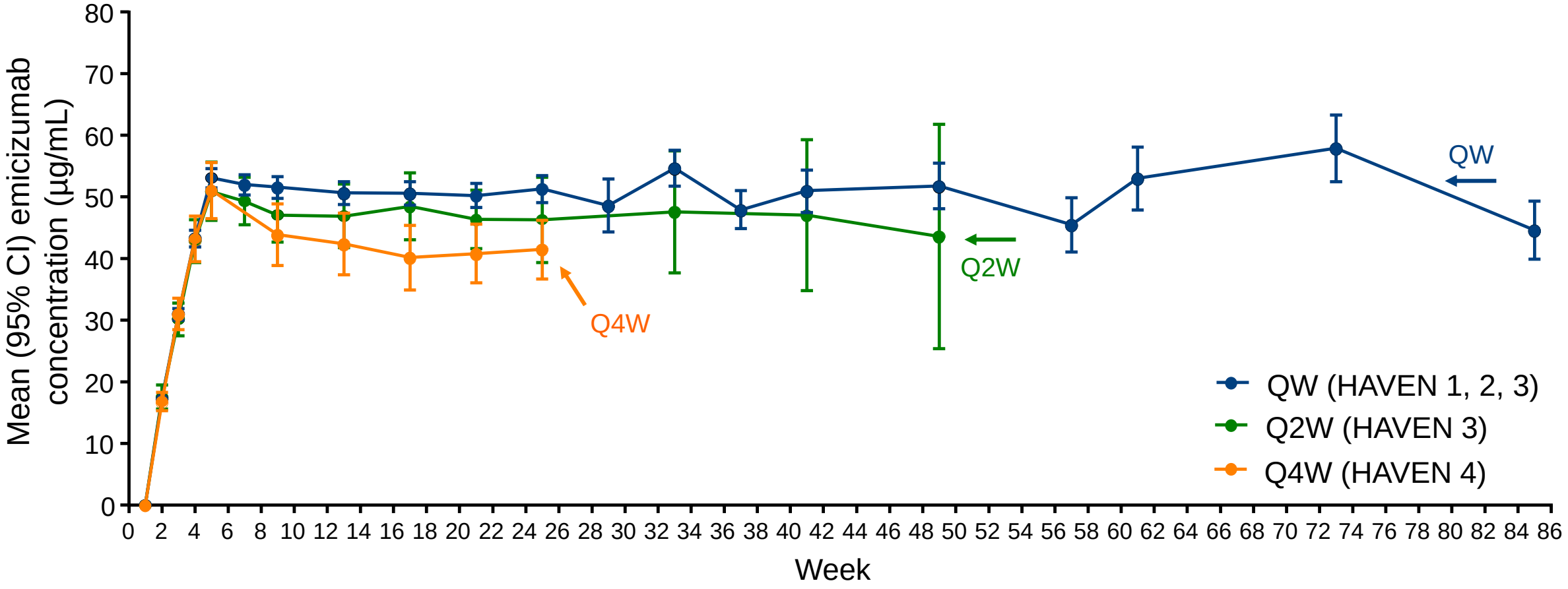
HAVEN 4: Patient preference
All patients preferred emicizumab



- EmiPref survey was completed by all 41 (100%) eligible patients
- 100% (95% CI, 91.4; 100.0) of patients preferred emicizumab

IV, intravenous; SC, subcutaneous.

HAVEN 1 – 4: Emicizumab pharmacokinetics
Trough concentrations by dosing regimen (QW, Q2W and Q4W)



- Clinically efficacious concentrations obtained with all 3 dosing regimens (consistent with PK model predictions)
- For Q4W, emicizumab mean trough concentrations were maintained at ~41 µg/mL from Week 13 to Week 25

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HAVEN 4
Favourable safety profile observed with emicizumab

	Emicizumab 6 mg/kg Q4W N=41
Total number of AEs	148
Total patients ≥1 AE, n (%)	30 (73.2)
Serious AE*	1 (2.4)
Grade ≥3 AE	1 (2.4)
Related AE	12 (29.3)
Local injection-site reaction	9 (22.0)
AEs of special interest, n (%)	
Hypersensitivity	0
TE/TMA	0

- 73.2% of patients experienced ≥1 AE
- Only 1 serious (Grade ≥3) AE of rhabdomyolysis unrelated to emicizumab
- Injection-site reaction was the most common emicizumab-related AE (22.0%)
- No AEs led to emicizumab discontinuation or withdrawal
- No TEs, TMAs or hypersensitivity reactions
- No ADAs detected; no patients developed *de novo* FVIII inhibitors

Data cutoff: 15 Dec 2017.
*1 serious AE in the PK run-in cohort: grade 3 hypertension in patient with medical history of hypertension; unrelated to emicizumab treatment.

TE, thromboembolism; TMA, thrombotic microangiopathy.

HAVEN 4
Conclusions

- Emicizumab Q4W was safe and efficacious in PwHA ≥12 years with and without inhibitors
- Efficacy results were consistent across bleed-related endpoints and with other HAVEN studies
- Emicizumab was associated with a numerical improvement in Haem-A-QoL Physical Health domain score
- All patients preferred emicizumab over their prior haemophilia treatment
- Pharmacokinetic profiles support the efficacy data and were consistent with predictions
- Emicizumab showed a favourable safety profile with no TEs or TMAs
  - Most common AEs consistent with prior experience
  - Incidence of injection-site reaction in line with other HAVEN studies and mainly mild to moderate
  - No ADAs or *de novo* FVIII inhibitors detected

Yoneyama K, et al. *Clin Pharmacokinet* 2017 Epub.

Co-authors

- Victor Jiménez-Yuste: Hospital Universitario La Paz, Autónoma University, Madrid, Spain
- Amy Shapiro: Indiana Hemophilia and Thrombosis Center, Indianapolis, IN, USA
- Nigel Key: University of North Carolina, Chapel Hill, NC, USA
- Maria Podolak-Dawidziak: Medical University Department of Hematology, Wroclaw, Poland
- Cedric Hermans: Cliniques Universitaires St-Luc, Brussels, Belgium
- Kathelijne Peerlinck: UZ Leuven Gasthuisberg, Leuven, Belgium
- Michaela Lehle, Sammy Chebon, Agnes Portron and Nives Selak Bienz: F. Hoffmann-La Roche Ltd., Basel, Switzerland
- Gallia G. Levy: Genentech Inc., South San Francisco, CA, USA
- Midori Shima: Nara Medical University, Department of Pediatrics, Kashihara, Japan

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    - This study was co-sponsored by F. Hoffmann-La Roche Ltd. and Chugai Pharmaceutical Co., Ltd.
- Writing assistance was provided by Daniella Babu, PhD, of Envision Pharma Group, and funded by F. Hoffmann-La Roche Ltd.

HAVEN 4: Phase 3 study of emicizumab prophylaxis given every 4 weeks in persons with hemophilia A with and without inhibitors

Additional comments

Pivotal trials demonstrate robust safety profile of Hemlibra

No new safety events of concern

Event	HAVEN 1 N=112	HAVEN 2 N=60	HAVEN 3 N=150	HAVEN 4 N=41
Total number of AEs, n	457	201	543	148
Total patients ≥1 AE, n (%)	96 (85.7)	40 (66.7)	127 (84.7)	30 (73.2)
Serious AE, n (%)	19 (17.0)	6 (10.0)	14	1 (2.4)
TMA	3 (2.7)	0	0	0
TE	2 (1.8)	0	0	0
Fatal AEs, n (%)[1]	1 (0.9)	0	0	0
AEs leading to withdrawal, n (%)	3 (2.7)	0	1 (0.7)	0
Local injection-site reaction, n (%)	16 (14.3)	10 (16.7)	38 (25.3)	9 (22.0)

No TMA/TE events reported in persons without inhibitors on Hemlibra;
In persons with inhibitors, BPA treatment guidance is in place to treat breakthrough bleeds in patients on Hemlibra.

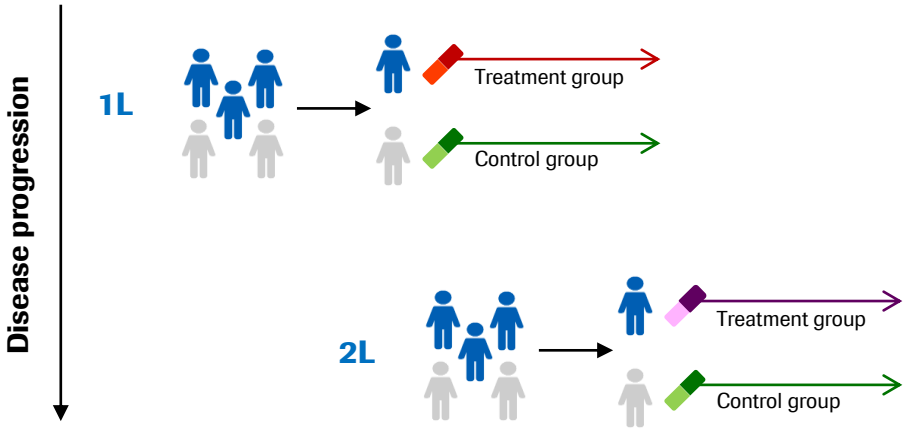
[1]HAVEN 1: Mancuso et al. ASH 2017 (data cutoff: 8 Sep 2017); [2]HAVEN 2: Young et al. ASH 2017 (data cutoff: 8 May 2017); [3]HAVEN 3: Mahlangu et al. WFH 2018 (data cutoff: 15 Sep 2017); [4]HAVEN 4: Pipe et al. WFH 2018 (data cutoff: 15 Dec 2017; Efficacy period for interim analysis: 25.8 weeks (24.1-29.4))
AE=adverse event; TMA=thrombotic microangiopathy; TE=thromboembolic event

Randomized trials vs. intra-individual comparison

Intra-individual comparison is a robust trial design in hemophilia A

Randomized trial

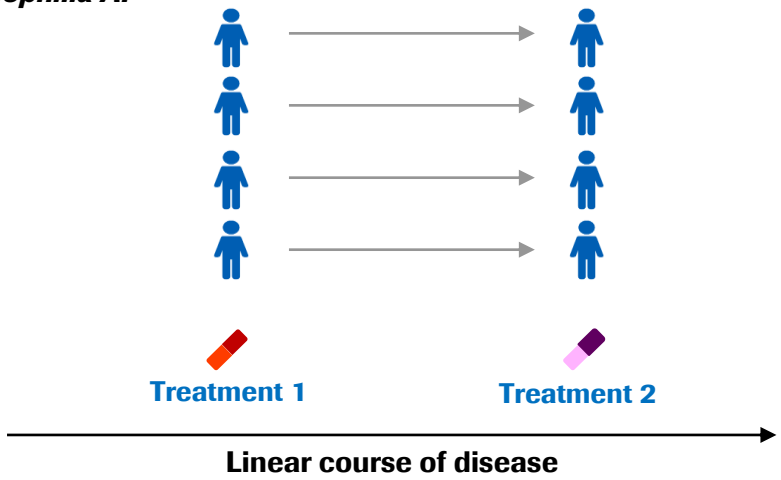
i.e. Oncology:



- Gold standard and suitable for both progressive and non-progressive diseases
- Aims to equalize distribution of known and unknown prognostic factors to each arm
- Allows for placebo control in cases where this is feasible and acceptable
- Might not fully balance all prognostic factors; does not tease out impact of one therapy vs another at a patient level

Intra-individual comparison

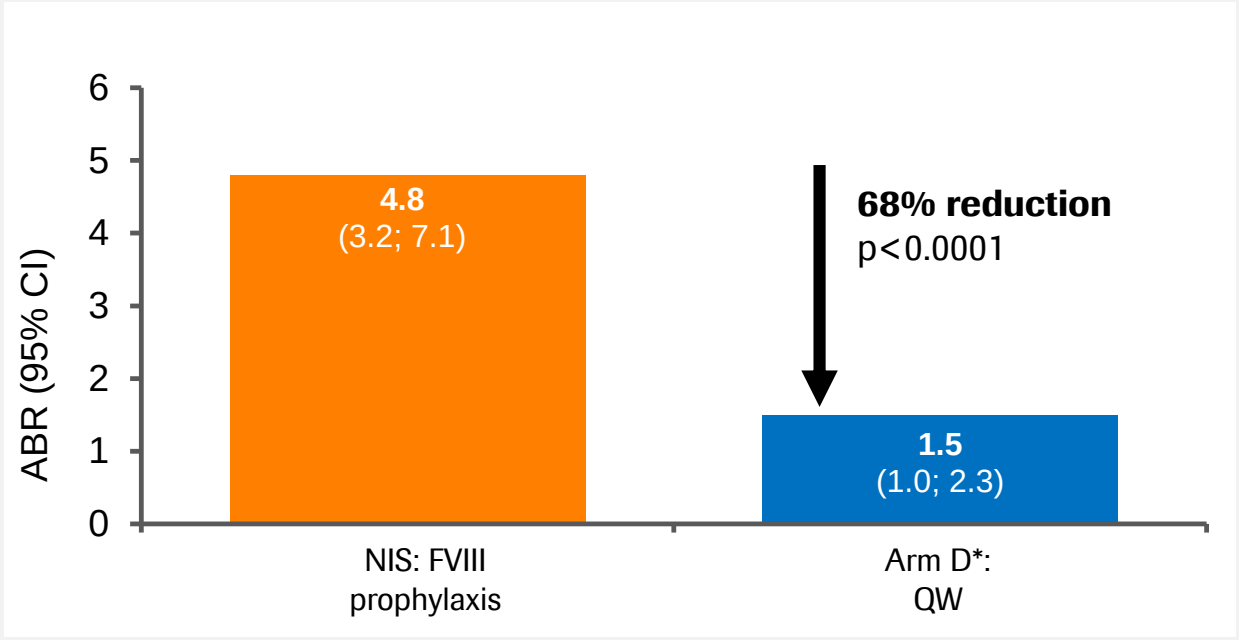
i.e. Hemophilia A:



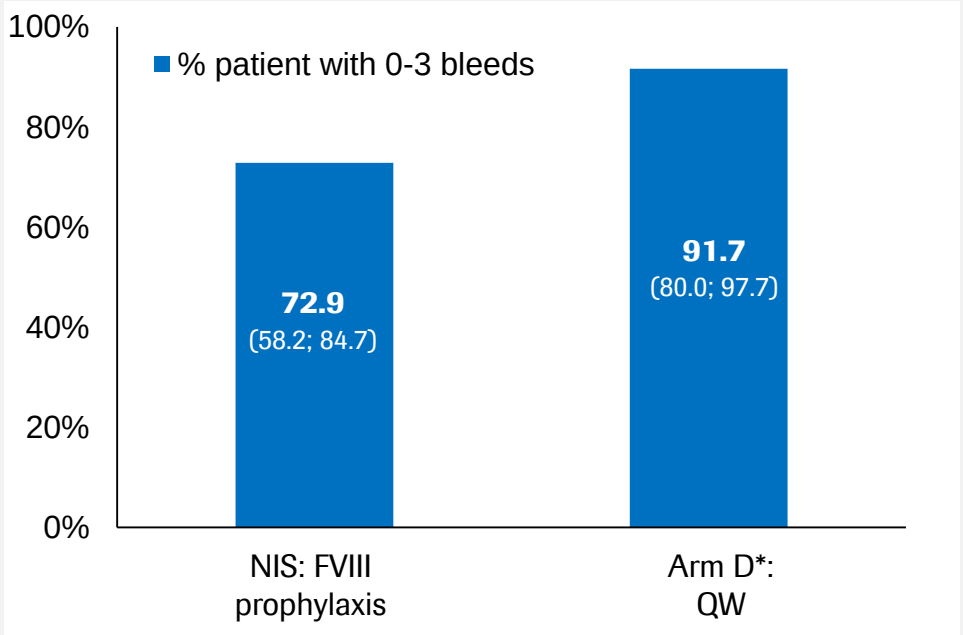
- Feasible only for non-progressive disease
- Known and unknown prognostic factors automatically balanced; controls for intra-patient variability
- Can measure impact at group level and patient level; important insights on how therapies differ in the same person

HAVEN 3 Arm D: Hemlibra prophylaxis showed superior efficacy as demonstrated by a significant reduction in treated bleeds

Treated bleeds – Hemlibra QW vs FVIII prophylaxis



Patients with 0–3 bleeds



Hemlibra prophylaxis resulted in a statistically significant reduction in treated bleeds of 68% compared to previous treatment with FVIII prophylaxis

Mahlangu et al. WFH 2018; data cutoff 15 Sept 2017
*Data from 48 patients in Arm D who participated in the NIS shown.
ABR=annualised bleed rate; CI=confidence interval; F=factor; NIS=non-interventional study; QW=once-weekly administration; Q2W=administered every 2 weeks

FVIII prophylactic therapies: Results of Phase 3 studies

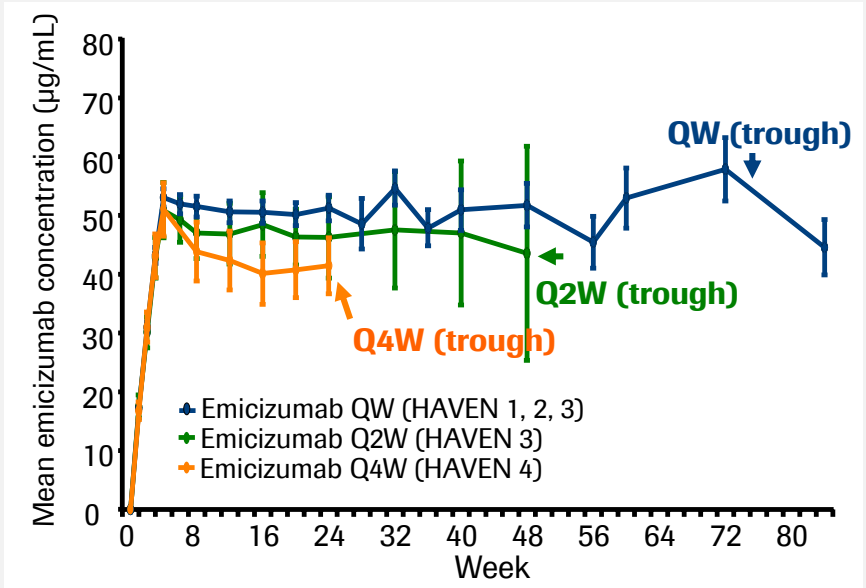
Brand name	Frequency of IV administration	N	Mean ABR (95% CI or ± SD)	Median ABR (IQR or range)	% patients zero bleeds	Reference
NIS: Standard or extended half-life FVIII						
		48	**4.8** (3.2; 7.1)**	**1.8 (0.0, 7.6)**	**39.6%**	
Standard half-life FVIII						
Advate®	Q2d	30 (std)	1.6 (± 1.2)	1 (2.1) †	42%	Advate USPI, Valentino et al. 2012
		23 (PK)	1.9 (± 1.1)	1 (4.1) †		
NovoEight®	3x/wk or Q2d	213	6.5 (5.3, 8)	3.1 (7.3) †	–	NovoEight USPI, Lentz et al. 2013
Nuwiq®	3x/wk or Q2d	32 (adult)	2.3 (± 3.7)	0.9 (0–14.7)	50%	Nuwiq USPI, Lissitchkov et al. 2015
		59 (peds)	4.1 (± 5.2)	1.9 (0–20.7)	33.9%	
Kovaltry®	2x/wk	18	3.8 (± 5.2)	1 (0, 8)	37.5% ‡	Kovaltry USPI, Saxena et al. 2016, Kavakli et al. 2015
	3x/wk	44		2 (0.5, 5)	62.5% ‡	
	2x/wk	28	4.9 (± 6.8)	4 (0, 8)	28.6%	
	3x/wk	31		2 (0, 4.9)	25.8%	
Afstyla®	2–3x/wk	146	3.1 (± 5.1)	1.1 (0, 4.2)	43%	Afstyla USPI, Mahlangu et al. 2016
Extended half-life FVIII						
Eloctate®	Q3-5d	117	2.9 (2.3, 3.7)	1.6 (0, 4.7)	45%	Eloctate USPI, Mahlangu et al. 2014
Adynovate®	2x/wk	120 (ITT)	4.7 (± 8.6)	1.9 (0, 5.8)	38%	Adynovate USPI, Konkle et al. 2015
Bay 94-9027*	Q5d	43	–	1.9 (0, 4.2)	–	Reding et al. 2017
	QW	43	–	3.9 (0, 6.5)	–	
	2x/wk	11	–	1.9 (0, 5.2)	–	
	2x/wk	13	–	4.1 (2, 10.6)	–	
N8-GP*	Q4d	175	3.7 (2.9; 4.7)	1.3 (0, 4.6)	40%	Giangrande et al. 2017

Cross-trial comparisons or claims of inferiority or superiority are not appropriate.
*Not an approved therapy. †IQR = difference between 75th percentile (3rd quartile) and 25th percentile (1st quartile), ‡Of a subgroup of 16 patients with observation of one-year treatment period.
ABR=annualized bleeding rate; F=factor; std/PK=standard (20–40 IU kg^{-1} every other day) or pharmacokinetic (PK)-tailored (20–80 IU kg^{-1} every third day) prophylaxis; ITT=intent to treat; Q2d=every two days; Q4d=every 4 days; Q5d=every 5 days; r=recombinant
**Estimated ABR by negative binomial model

Consistency of results from HAVEN studies demonstrate dosing flexibility with Hemlibra

Primary endpoint: Treated bleeds	HAVEN 1 Arm A N=35, qw	HAVEN 2 N=23, qw	HAVEN 3		HAVEN 4 N=41, q4w
			Arm A N=36, qw	Arm B N=35, q2w	
ABR, model based (95% CI)*	**2.9** (1.7; 5.0)	**0.2** (0.06; 0.62)	**1.5** (0.9; 2.5)	**1.3** (0.8; 2.3)	**2.4** (1.4; 4.3)
Reduction RR, P-value	**87% reduction**, 0.13, p<0.001 (vs Arm B)	NA	**96% reduction**, 0.04, p<0.0001 (vs Arm C)	**97% reduction**, 0.03, p<0.0001 (vs Arm C)	NA
Median ABR, calculated (IQR)	**0.0** (0.0; 3.7)	**0.0** (0.00; 0.00)	**0.0** (0.0; 2.5)	**0.0** (0.0; 1.9)	**0.0** (0.0; 2.1)
Zero bleeds, % pts (95% CI)	**62.9** (44.9; 78.5)	**87.0** (66.4; 97.2)	**55.6** (38.1; 72.1)	**60.0** (42.1; 76.1)	**56.1** (39.7; 71.5)

Trough concentrations by dosing regimen



Clinically efficacious concentrations obtained with all 3 dosing regimens

[1]HAVEN 1: Oldenburg J, et al. N Engl J Med 2017;377:809–18 (data cutoff: 25 Oct 2016); [2]HAVEN 2: Young et al. ASH 2017 (data cutoff: 8 May 2017); [3]HAVEN 3: Mahlangu et al. WFH 2018 (data cutoff: 15 Sep 2017); [4]HAVEN 4: Pipe et al. WFH 2018 (data cutoff: 15 Dec 2017; Efficacy period for interim analysis: 25.8 weeks (24.1-29.4)); *ABR calculated with negative binomial regression model
ABR=annualised bleed rate; CI=confidence interval; Q4W=administered every 4 weeks; IQR=interquartile range

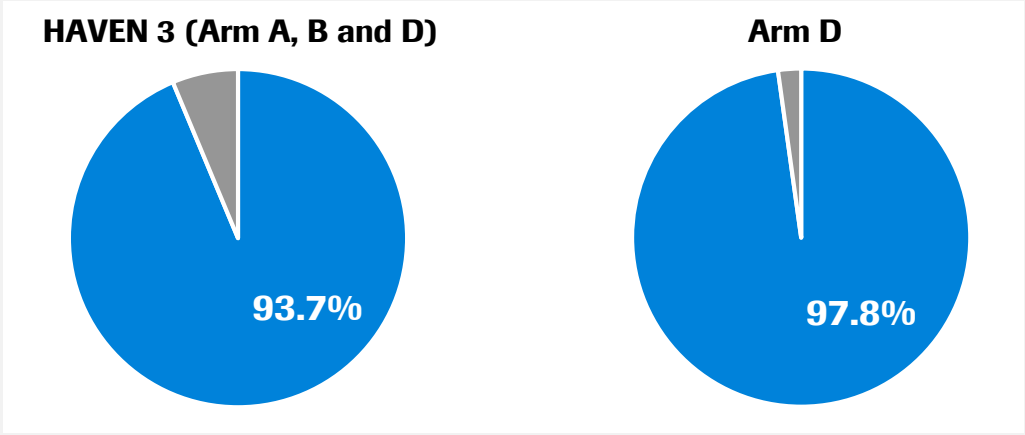
Greater than 93% of patients preferred Hemlibra over their prior therapy

Which of the treatments would you prefer to take as the treatment for your hemophilia?

- ❑ Prefer my old hemophilia treatment (IV)
- ❑ Prefer Hemlibra treatment (SC)
- ❑ Have no preference

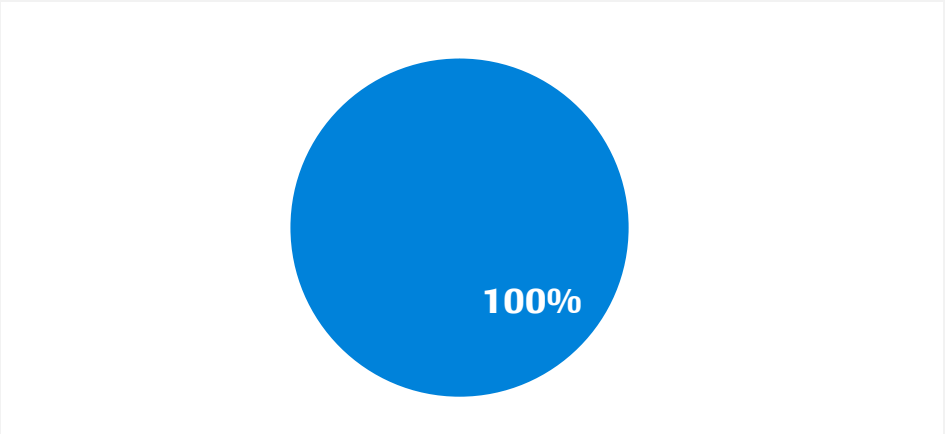
HAVEN 3

Survey was completed by 95/134 (70.9%) eligible patients (Arms A, B and D)



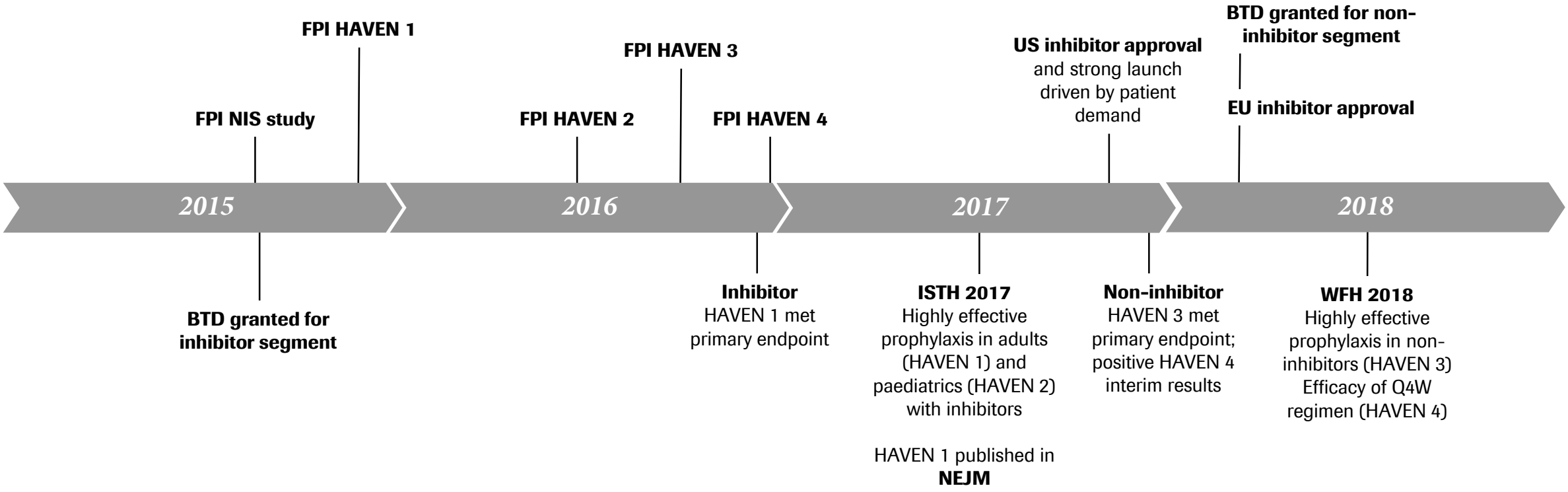
HAVEN 4

Survey was completed by all 41 (100%) eligible patients



Mahlangu et al. WFH 2018, Pipe et al. WFH 2018
Exploratory efficacy endpoint assessed patient preference using the EmiPref survey

Hemlibra: A success story



- ✓ Two BTDs granted by FDA
- ✓ Robust development program demonstrated efficacy in people with Hemophilia A with and without inhibitors to FVIII
- ✓ Subcutaneous dosing offers flexibility (qw, q2w and q4w)
- ✓ Robust safety profile

Doing now what patients need next