R&Dカンファレンスコール（WFH2018）
HAVEN 3試験　／　HAVEN 4試験

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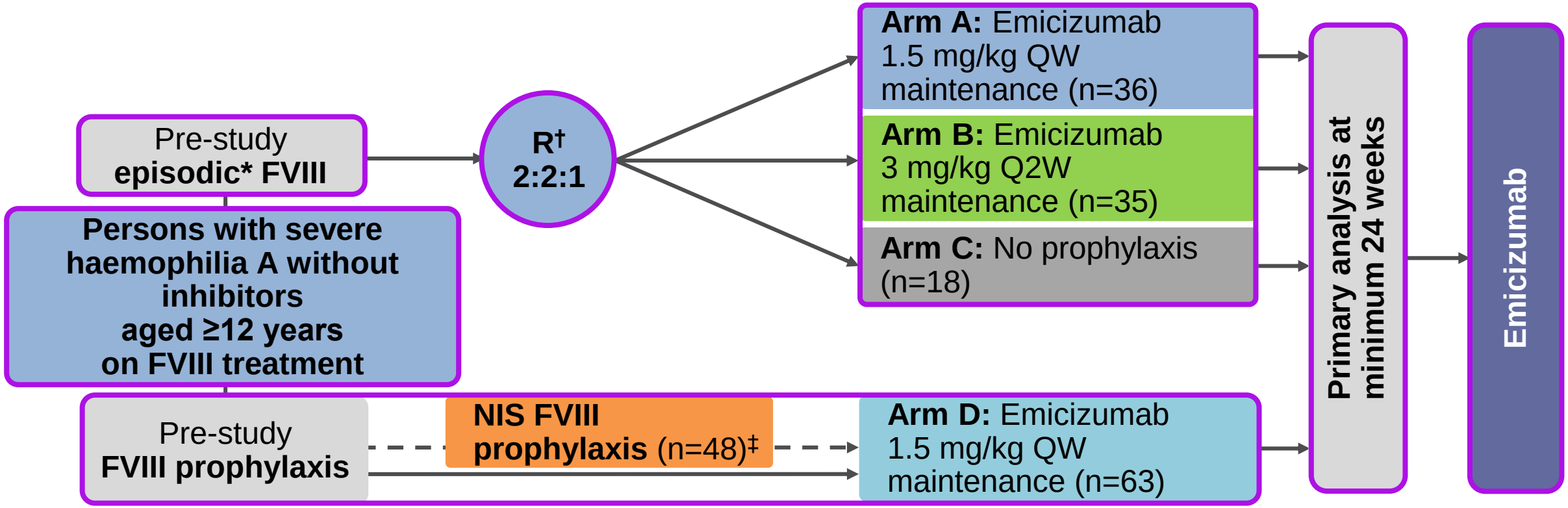
HAVEN 3試験結果

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

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.

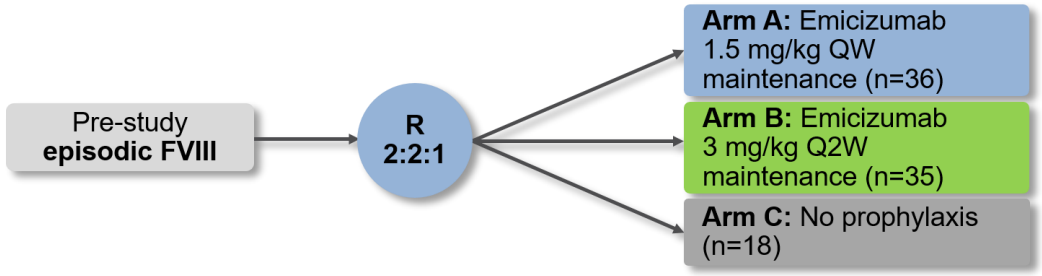
HAVEN 3: Demographics and baseline clinical characteristics

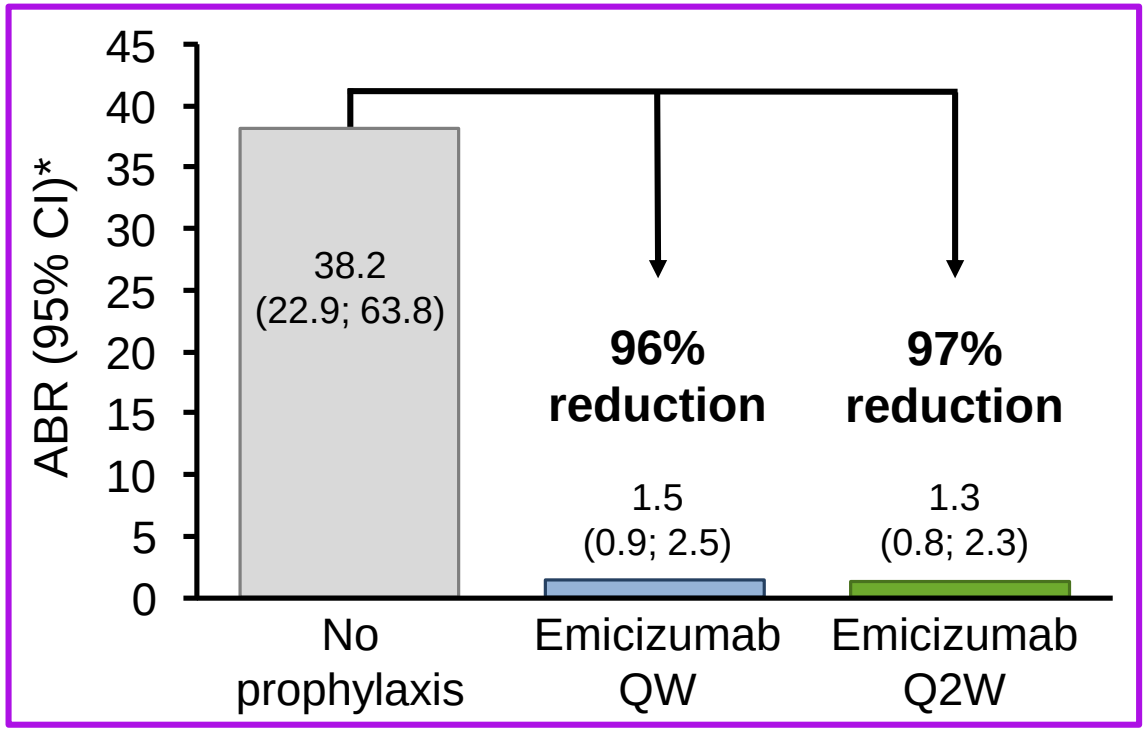
	Prior episodic treatment			Prior prophylaxis	
Characteristic	**Arm A: Emicizumab 1.5 mg/kg QW n=36**	**Arm B: Emicizumab 3 mg/kg Q2W n=35**	**Arm C: No prophylaxis n=18**	**Arm D: Emicizumab 1.5 mg/kg QW n=63**	**Total N=152**
Median (min–max) age, years	36.5 (19–77)	41.0 (20–65)	40.0 (16–57)	36.0 (13–68)	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.

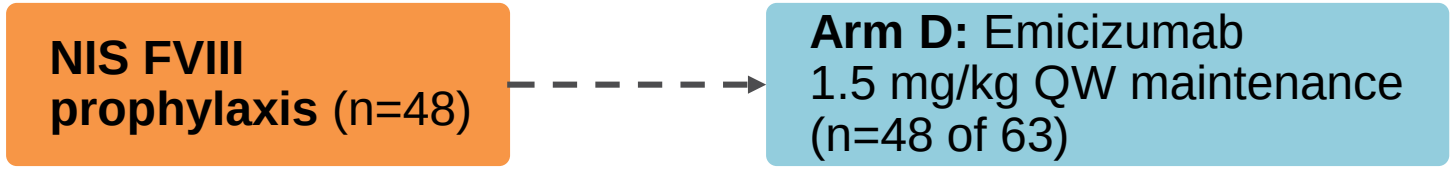
HAVEN 3 bleed-related secondary endpoints

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.

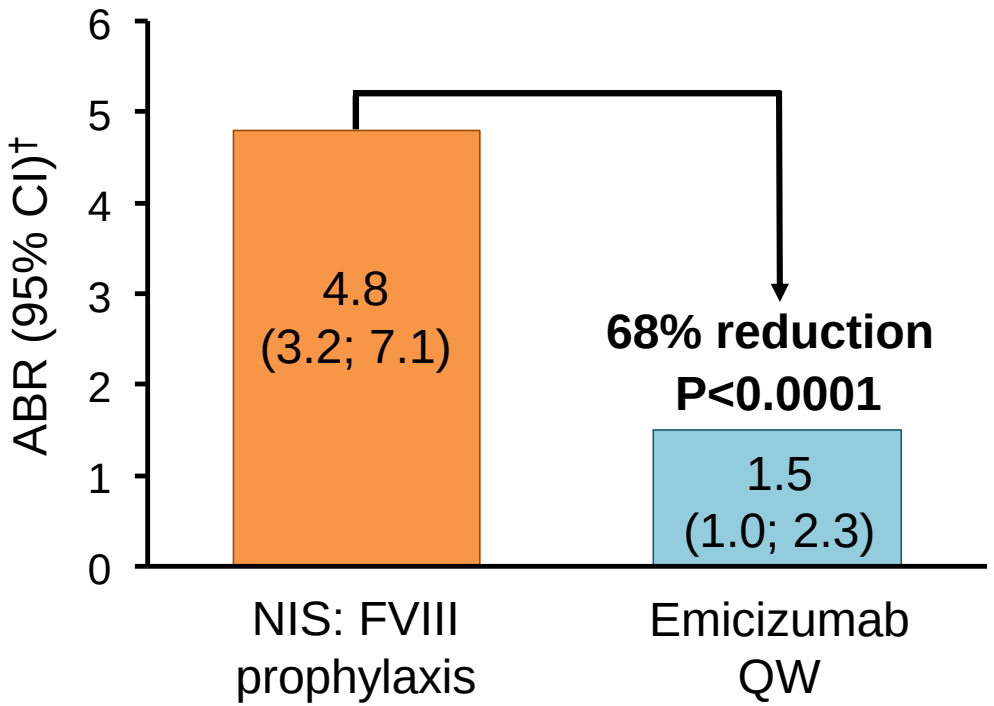
HAVEN 3: Intraindividual comparison methods



- 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

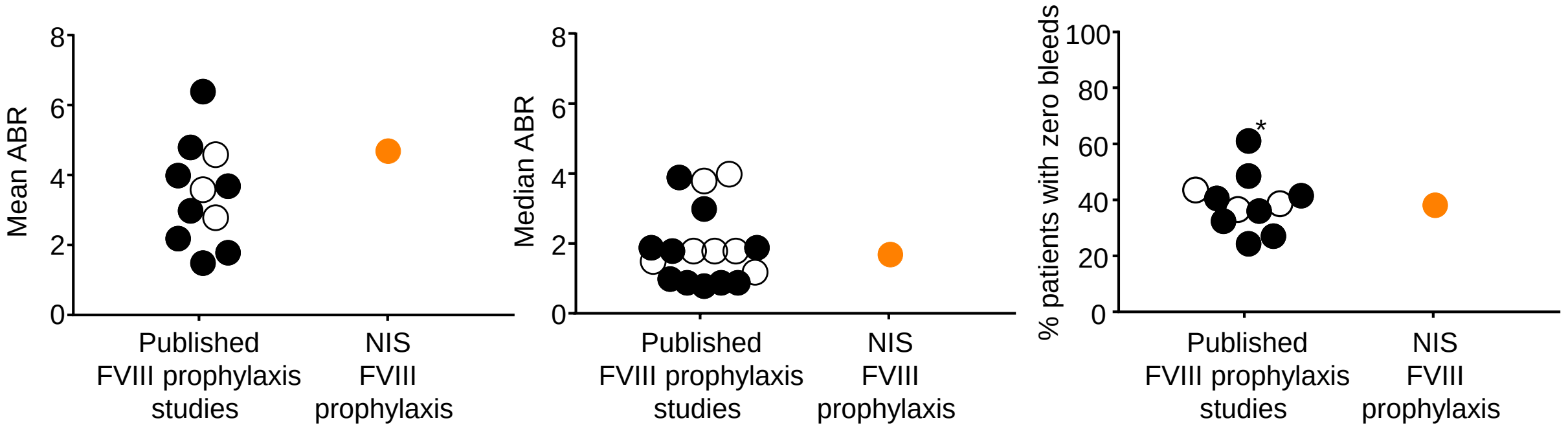
Endpoint	Arm D: Emicizumab 1.5 mg/kg QW n=48*	NIS: FVIII prophylaxis n=48
Duration of efficacy period, median (min-max), weeks	33.7 (20.1–48.6)	30.1 (5.0–45.1)
ABR, model based (95% CI)†	1.5 (1.0; 2.3)	4.8 (3.2; 7.1)
Reduction vs NIS FVIII RR, P-value	**68% reduction** 0.32, P<0.0001	—
Median ABR, calculated (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.

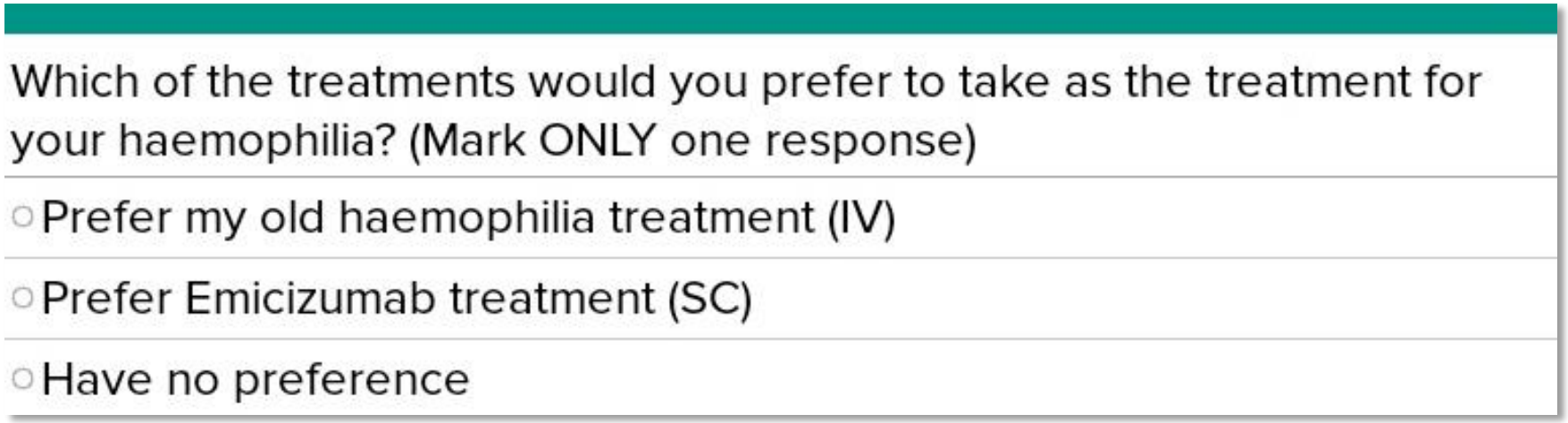
HAVEN 3: Haem-A-QoL Physical Health domain score
Emicizumab resulted in numerical improvement

	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.

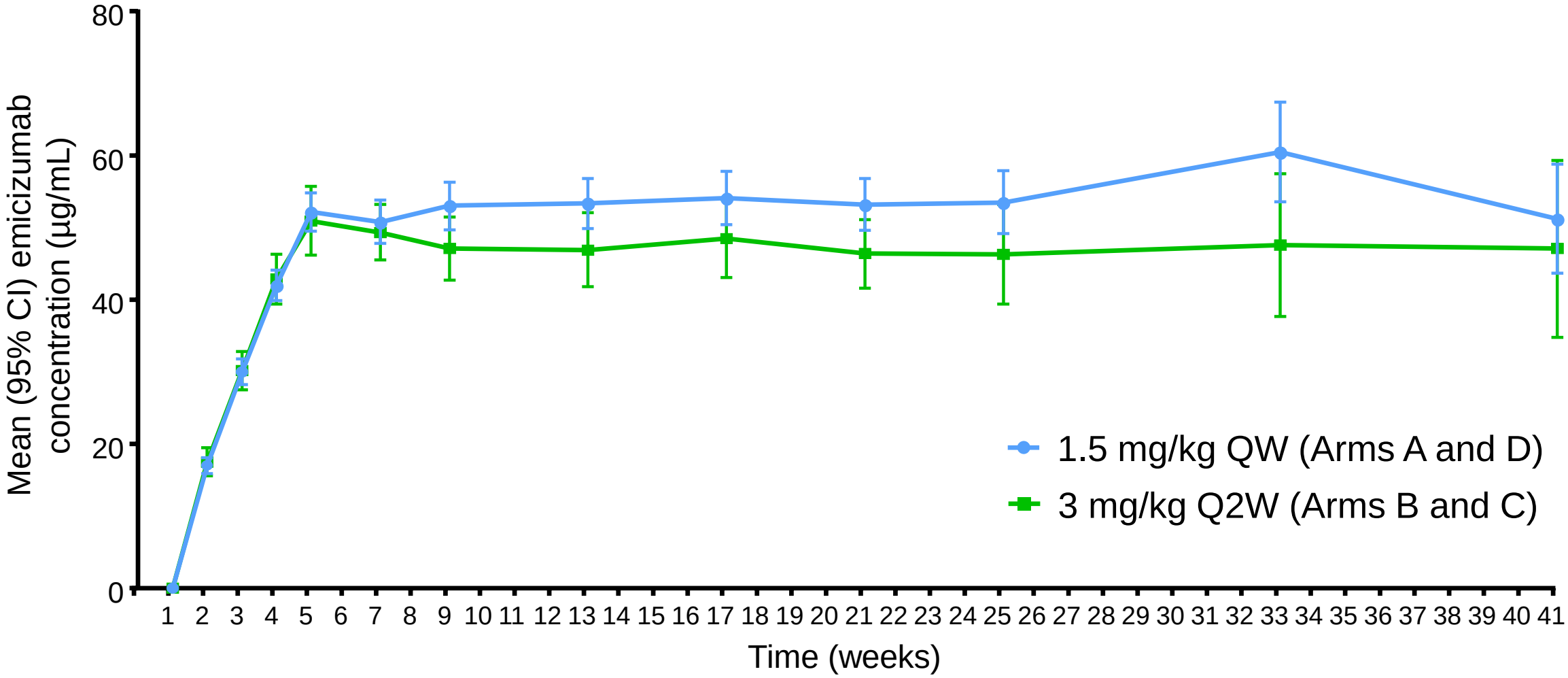
HAVEN 3: Safety summary
Favourable safety profile observed with emicizumab

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

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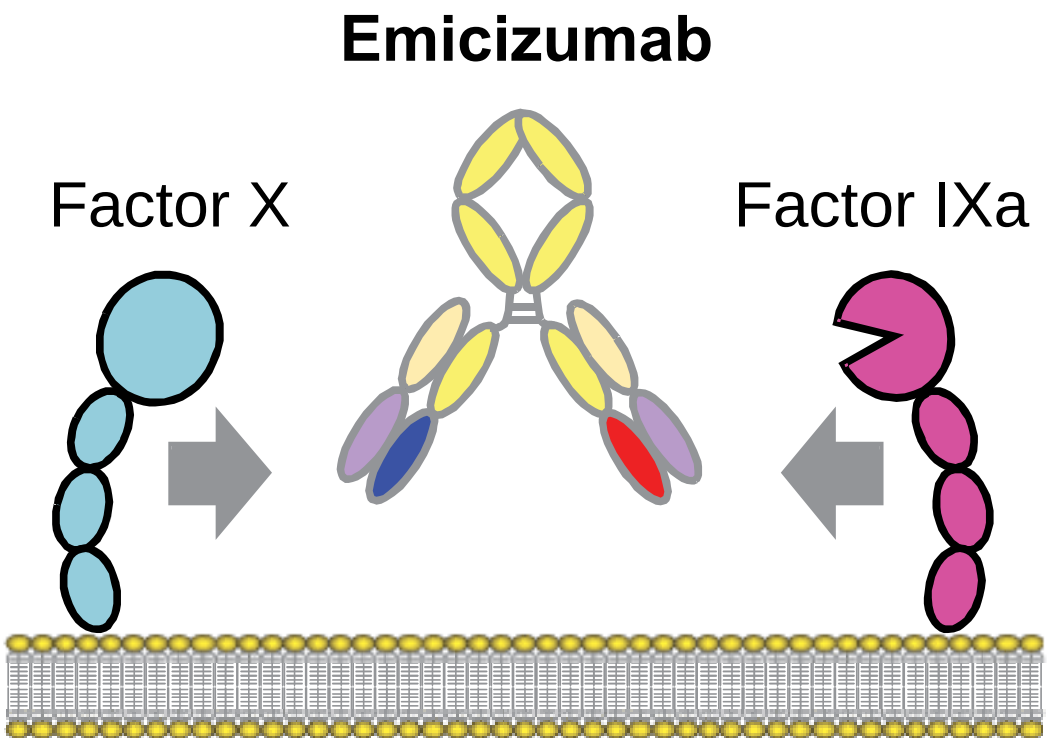
HAVEN 4試験結果

Background: Emicizumab



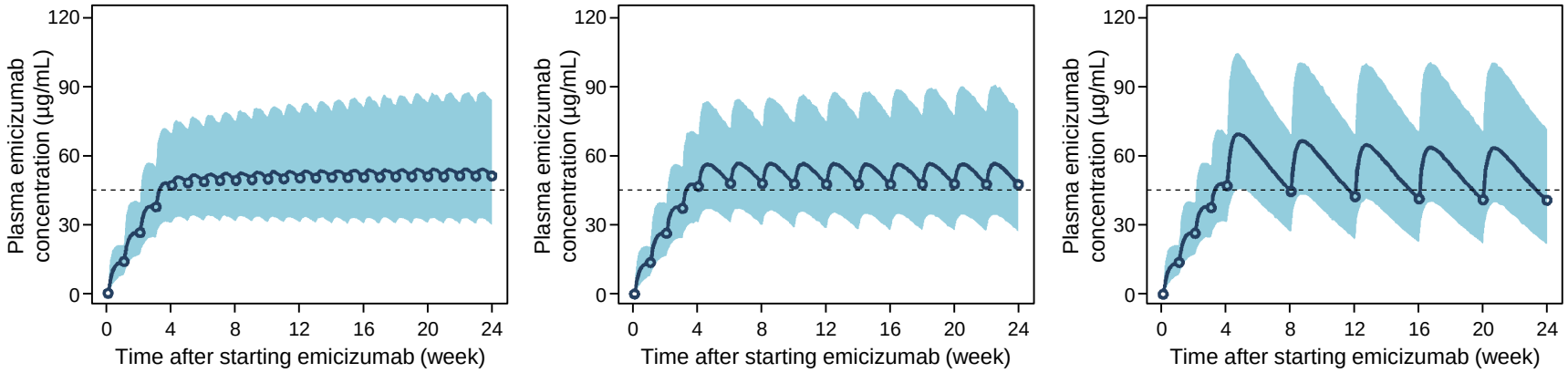
- Humanised bispecific monoclonal antibody
- Bridges activated factor IX (FIXa) and FX to restore function of missing FVIIIa
- No structural homology to FVIII (not expected to induce FVIII inhibitors or be affected by presence of FVIII inhibitors)
- Long half-life of ~30 days
- Administered subcutaneously
- 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.

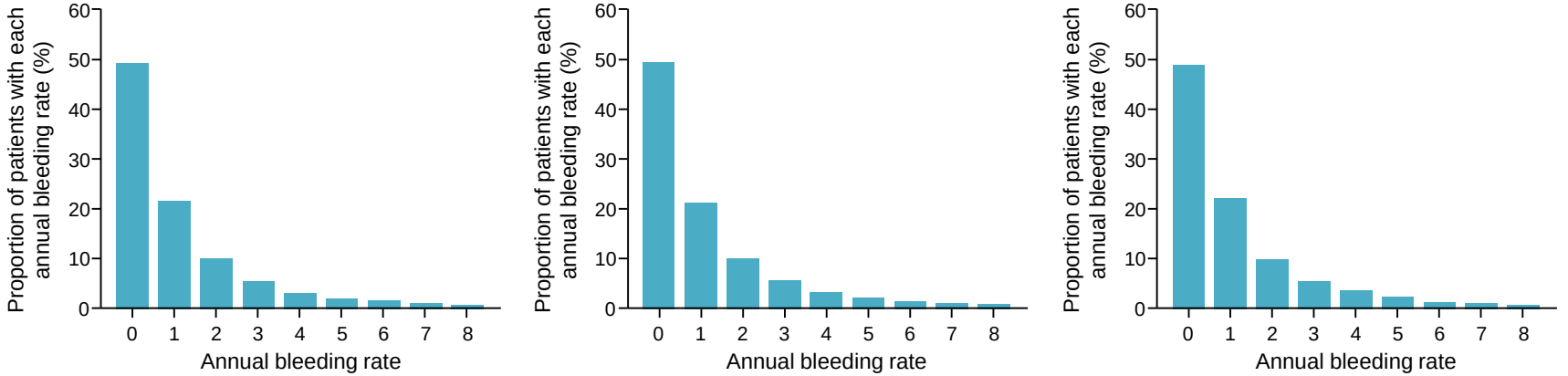
PK and efficacy modelling for different emicizumab dosing regimens

1.5 mg/kg QW | **3 mg/kg Q2W** | **6 mg/kg Q4W**

PK modelling



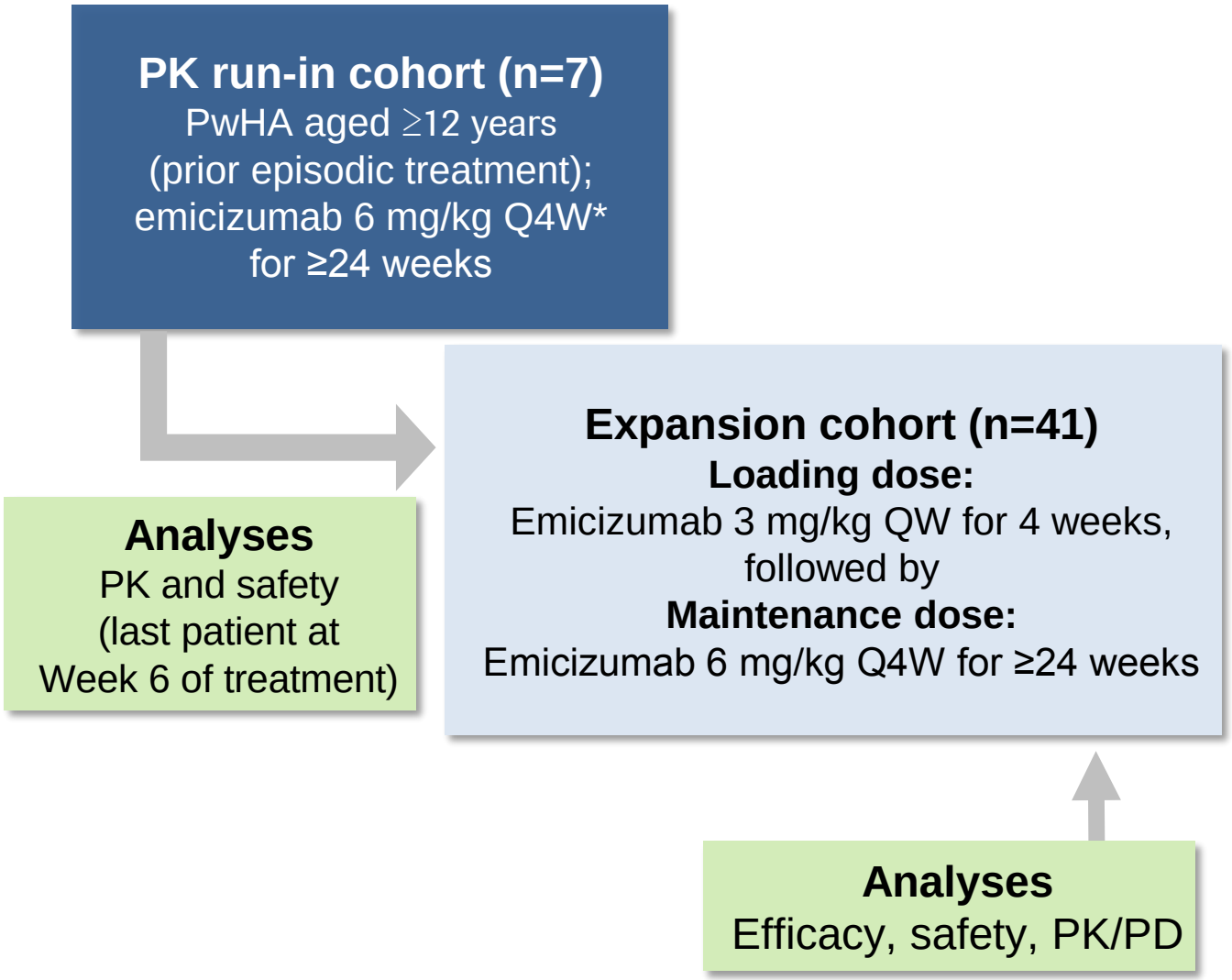
Modelled ABR



- 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

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

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

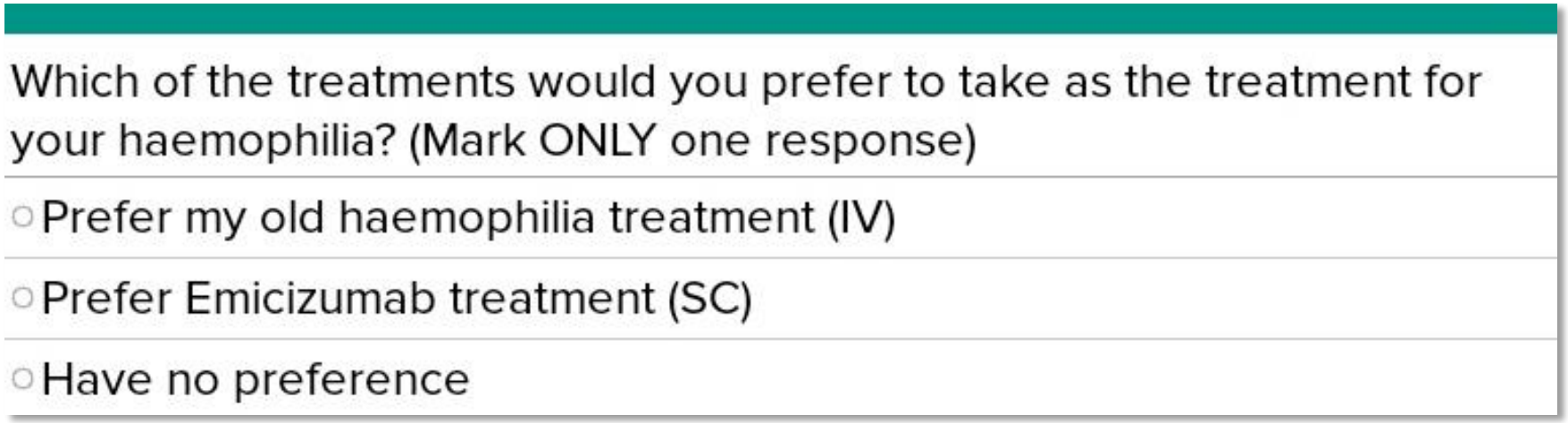
	Emicizumab 6 mg/kg Q4W N=38*	
	Baseline	**Week 25**
Patients, n	38	37
Physical Health domain score, mean (SD)	47.0 (25.1)	32.4 (25.4)
Change from baseline, mean (95% CI)	–	–15.1 (–22.4; –7.8)

- 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.

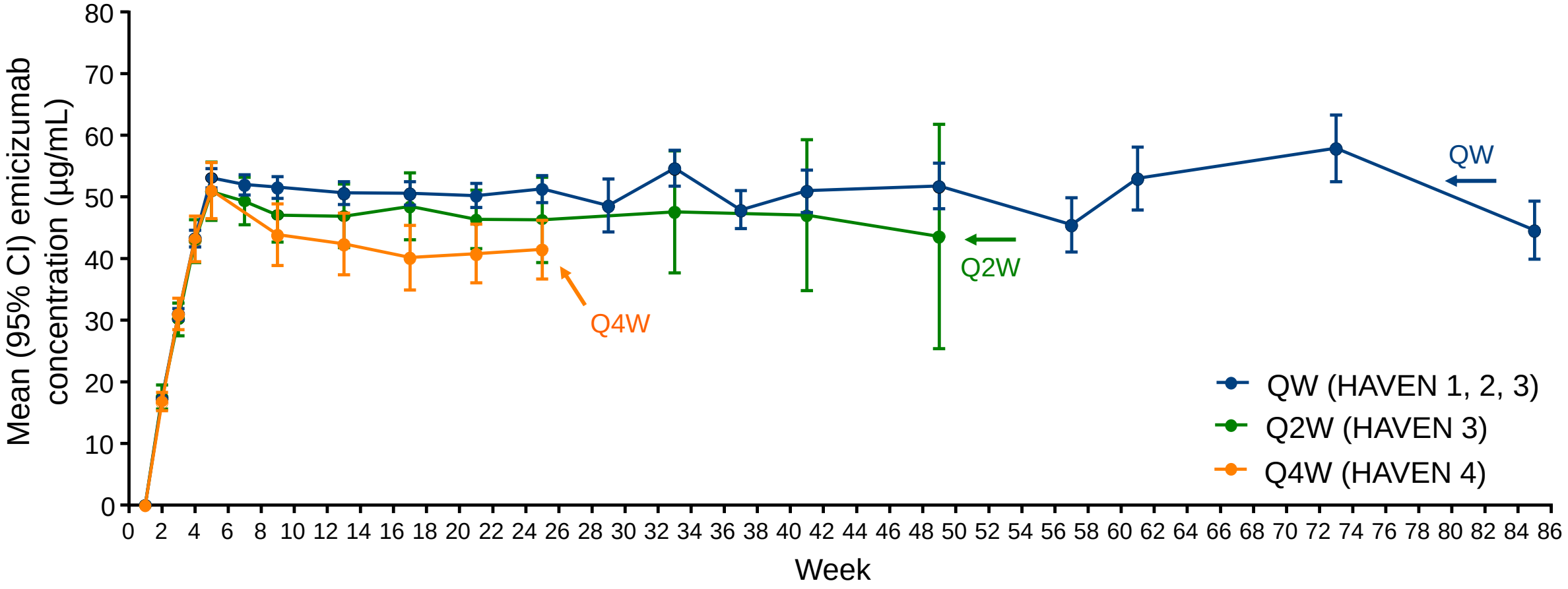
HAVEN 4: Patient preference
All patients preferred emicizumab



- 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

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

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

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