

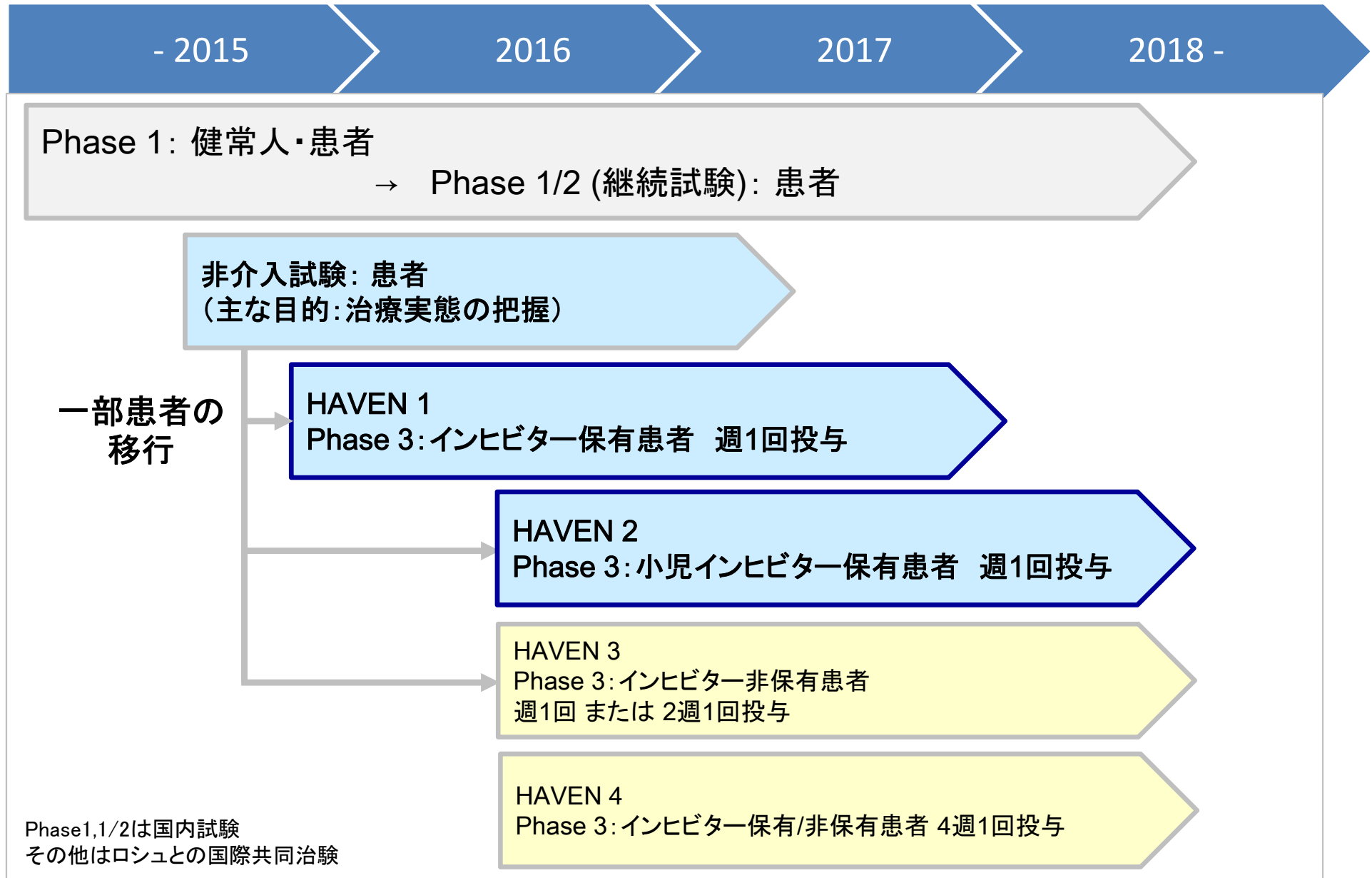
# 中外製薬R&Dコール (ISTH 2017)

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# ACE910/エミシズマブ 開発プログラム



# HAVEN 1試験 / HAVEN 2試験中間解析

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2017.7.11

# HAVEN 1: Emicizumab (ACE910) prophylaxis in patients with hemophilia A with inhibitors – a randomized, multicenter, open-label, phase 3 study to investigate efficacy, safety and pharmacokinetics

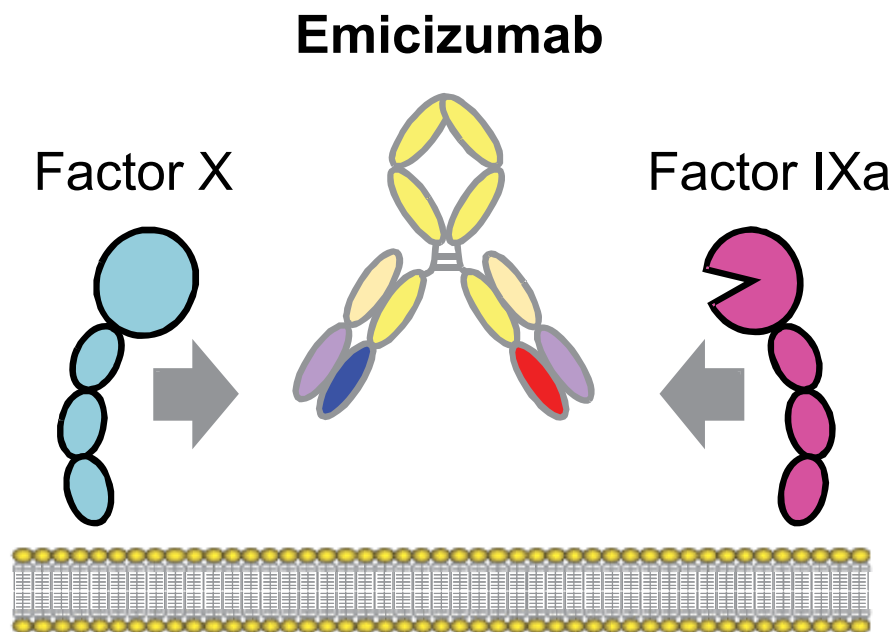
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*Emicizumab is an investigational product and is not approved or licensed for the treatment of patients with hemophilia A or any other medical condition*

# Emicizumab (ACE910)

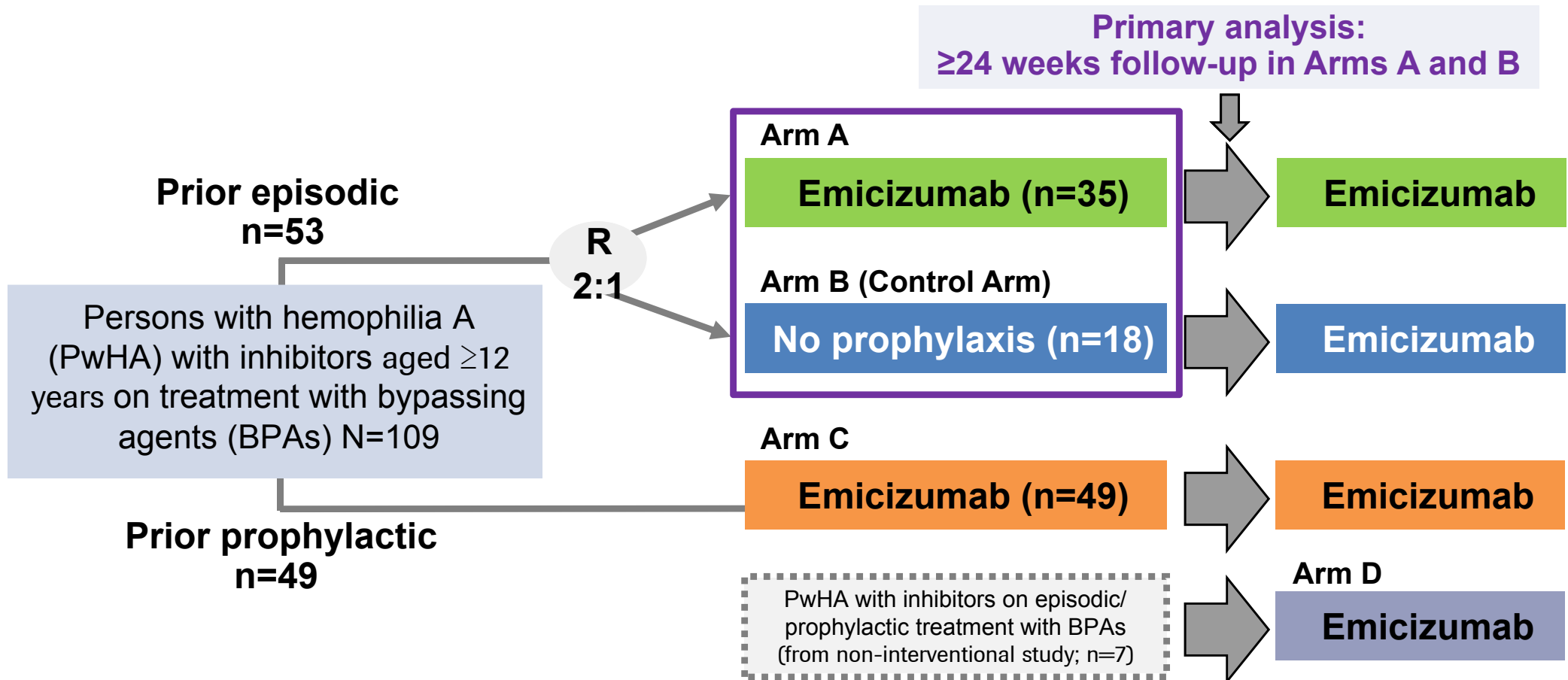
## Humanized bispecific monoclonal antibody



- Novel humanized 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
- Administered subcutaneously

# HAVEN 1 study design

## Once-weekly subcutaneous emicizumab prophylaxis



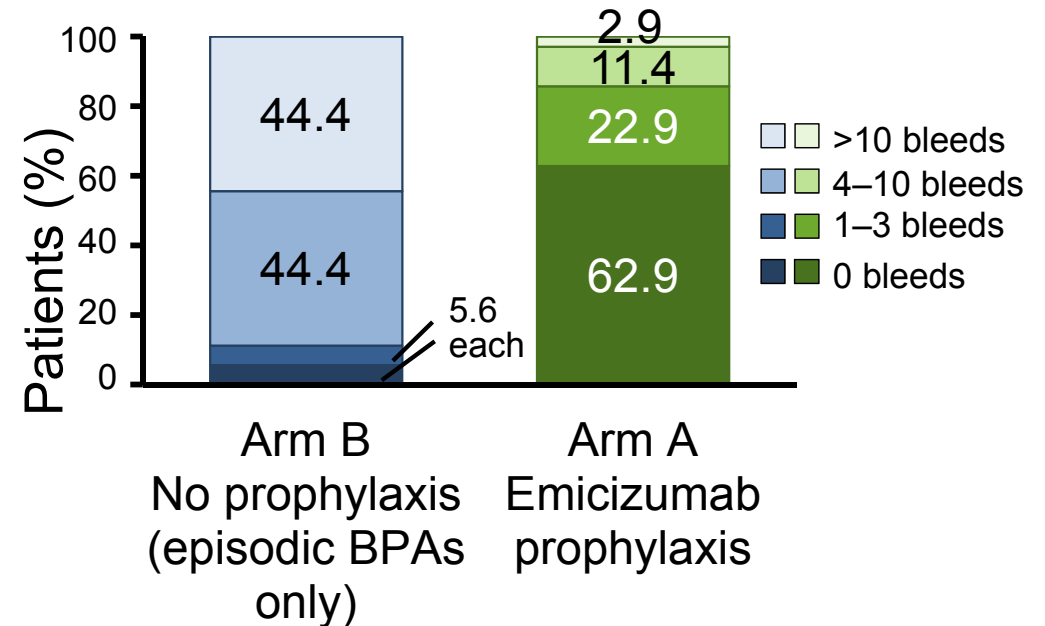
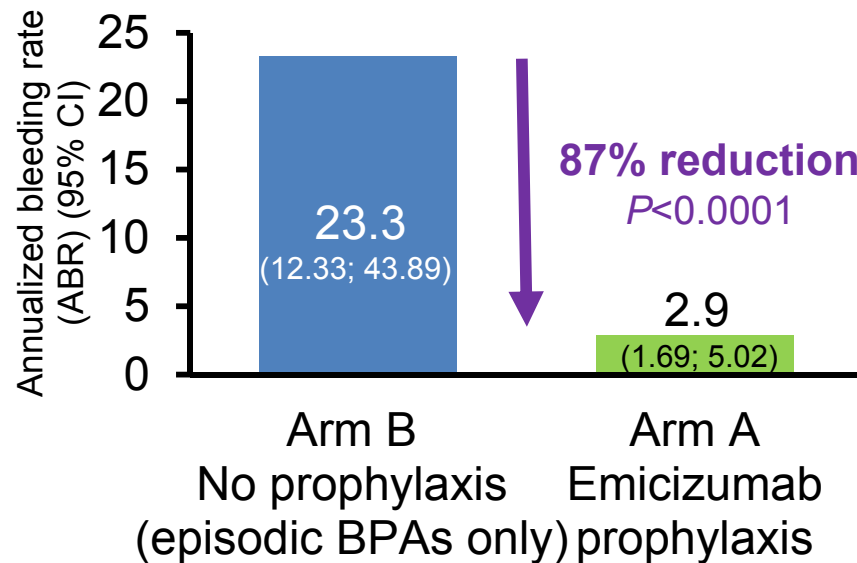
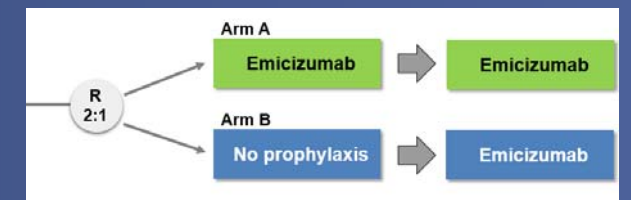
# HAVEN 1

## Demographics/baseline disease characteristics

	Arm A: Emicizumab prophylaxis (prior episodic BPAs) n=35	Arm B: No prophylaxis (prior episodic BPAs; control arm) n=18	Arm C: Emicizumab prophylaxis (prior BPA prophylaxis) n=49	Arm D: Emicizumab prophylaxis (prior BPAs; episodic or prophylactic) n=7	Total N=109
<b>Age</b>					
Median (range), years	38.0 (12–68)	35.5 (13–65)	17.0 (12–75)	26.0 (19–49)	28.0 (12–75)
<18 years, n (%)	4 (11.4)	2 (11.1)	26 (53.1)	0	32 (29.4)
<b>Bleeds in 24 weeks prior to study entry, n (%)</b>					
≥9	24 (68.6)	13 (72.2)	26 (53.1)	3 (42.9)	66 (60.6)
<b>Target joints, n (%)</b>					
Any	25 (71.4)	13 (72.2)	34 (69.4)	4 (57.1)	76 (69.7)
>1	18 (72.0)	10 (76.9)	24 (70.6)	1 (25.0)	53 (48.6)
<b>Highest historical inhibitor titer (BU)</b>					
Median	84.5 (n=32)	102.0 (n=16)	309.0 (n=47)	240.0 (n=6)	180.0 (n=101)
Range	5–1570	18–4500	11–5000	28–2125	5–5000
<b>Previously treated with ITI, n (%)</b>	14 (40.0)	7 (38.9)	33 (67.3)	3 (42.9)	57 (52.3)

# HAVEN 1 primary endpoint

## Randomized comparison of treated bleeds



Median ABR	<b>18.8</b>	<b>0.0</b>
(IQR)	<b>(12.97; 35.08)</b>	<b>(0.00; 3.73)</b>

- Statistically significant, clinically meaningful reduction in bleed rate with emicizumab
- 62.9% of patients experienced zero bleeds with emicizumab prophylaxis
- To date, no patients have discontinued due to lack of efficacy

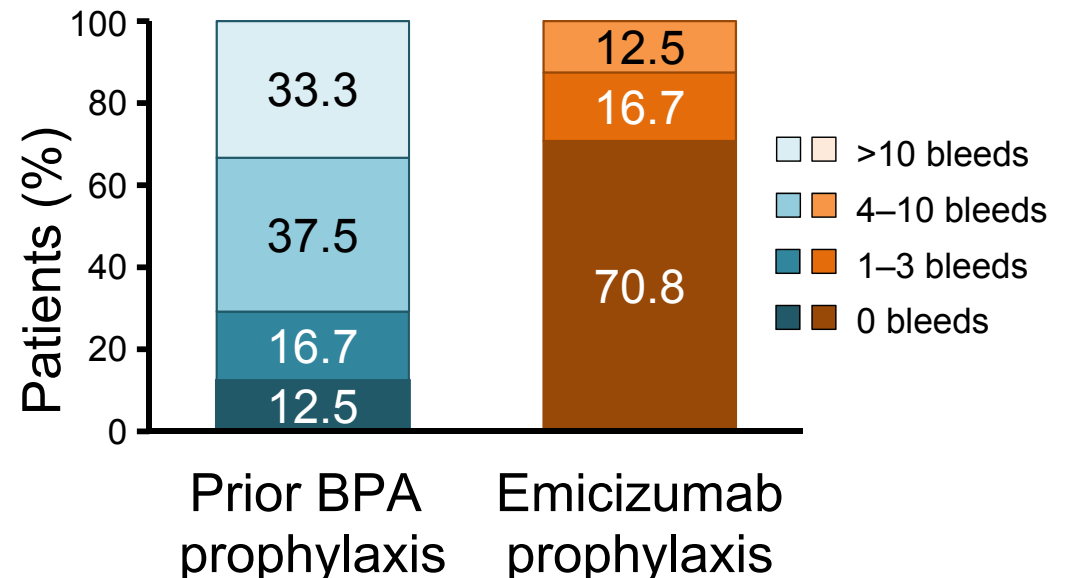
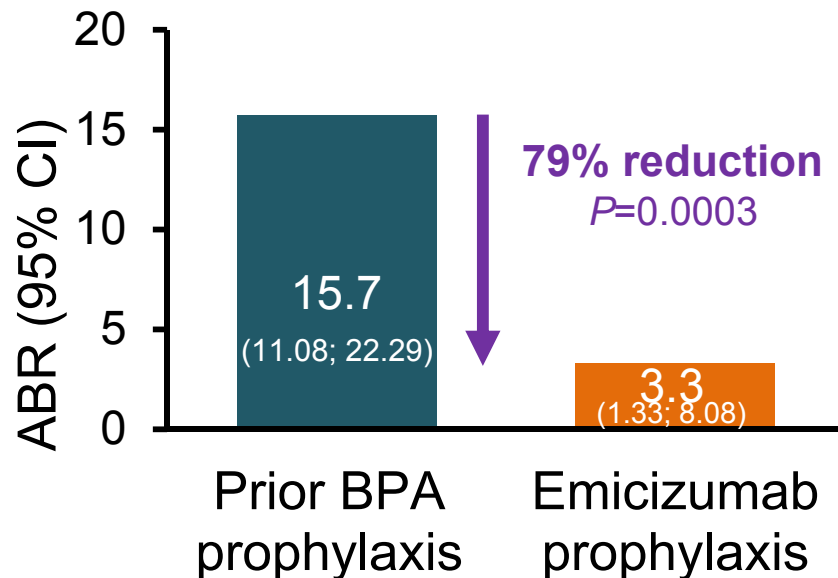
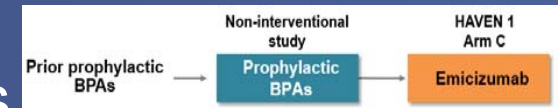


# HAVEN 1 secondary bleed-related endpoints

## Consistent statistically significant reductions in ABR

	Arm B: No prophylaxis (episodic BPAs) (n=18)	Arm A: Emicizumab prophylaxis (prior episodic BPAs) (n=35)
<b>All bleeds</b>		
ABR (95% CI)	28.3 (16.79; 47.76)	5.5 (3.58; 8.60)
% reduction (RR), <i>P</i> -value	<b>80% reduction (0.20), &lt;0.0001</b>	
% patients with 0 bleeds (95% CI)	5.6 (0.1; 27.3)	37.1 (21.5; 55.1)
<b>Treated spontaneous bleeds</b>		
ABR (95% CI)	16.8 (9.94; 28.30)	1.3 (0.73; 2.19)
% reduction (RR), <i>P</i> -value	<b>92% reduction (0.08), &lt;0.0001</b>	
% patients with 0 bleeds (95% CI)	11.1 (1.4; 34.7)	68.6 (50.7; 83.1)
<b>Treated joint bleeds</b>		
ABR (95% CI)	6.7 (1.99; 22.42)	0.8 (0.26; 2.20)
% reduction (RR), <i>P</i> -value	<b>89% reduction (0.11), 0.0050</b>	
% patients with 0 bleeds (95% CI)	50.0 (26.0; 74.0)	85.7 (69.7; 95.2)
<b>Treated target joint bleeds</b>		
ABR (95% CI)	3.0 (0.96; 9.13)	0.1 (0.03; 0.58)
% reduction (RR), <i>P</i> -value	<b>95% reduction (0.05), 0.0002</b>	
% patients with 0 bleeds (95% CI)	50.0 (26.0; 74.0)	94.3 (80.8; 99.3)

# Intra-individual comparison: treated bleeds with emicizumab prophylaxis vs prior BPA prophylaxis



Median ABR (IQR)	<b>12.0</b> (5.73; 24.22)	<b>0.0</b> (0.00; 2.23)
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- Statistically significant, clinically meaningful reduction in bleed rates with emicizumab prophylaxis vs prior BPA prophylaxis
- 70.8% of patients with zero bleeds on emicizumab prophylaxis

# HAVEN 1 health-related quality of life and health status

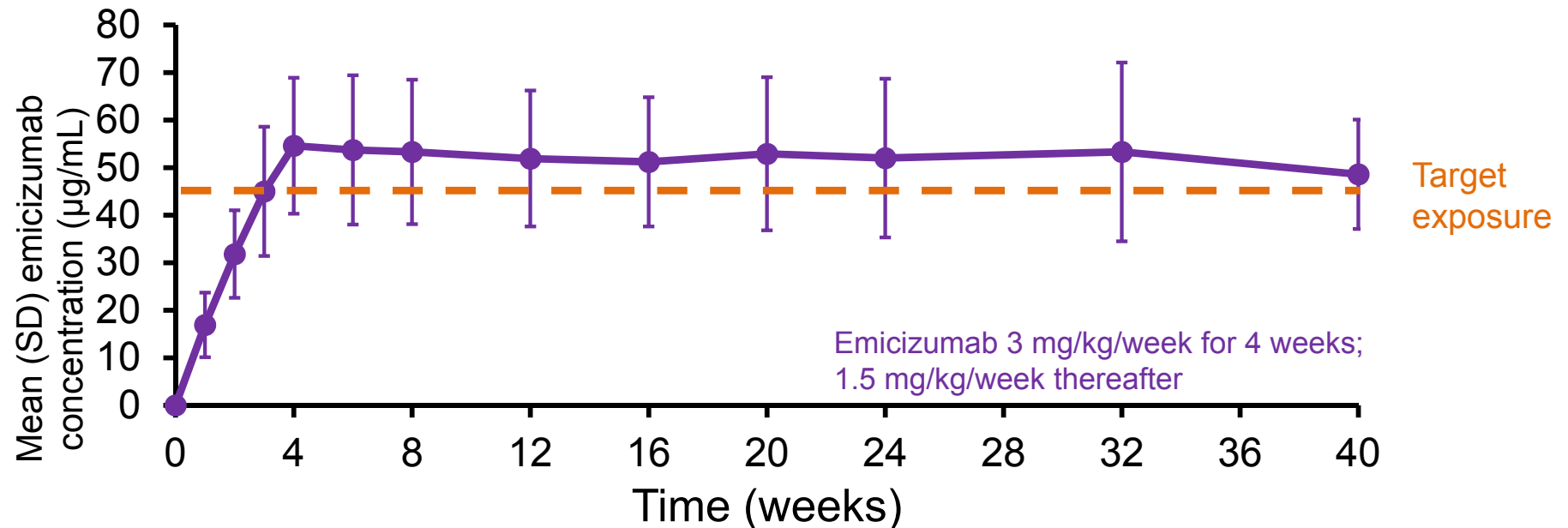
## Randomized comparison

Measure	Number of patients (Arm B/Arm A)	Clinically meaningful difference	Difference in adjusted means (95% CI) (Arm B vs Arm A)	P-value
<b>Haem-A-QoL</b> (in patients aged ≥18 years)				
Total score	14/25	+10 points	14.01 (5.56; 22.45)	0.0019
Physical health score	14/25	+7 points	21.55 (7.89; 35.22)	0.0029
<b>EQ-5D-5L</b>				
Visual analog scale	16/30	-7 points	-9.72 (-17.62; -1.82)	0.0171
Index utility score	16/30	-0.07 points	-0.16 (-0.25; 0.07)	0.0014

- Statistically significant, clinically meaningful improvements in HRQoL and health status with emicizumab prophylaxis vs no prophylaxis

# HAVEN 1

## Emicizumab pharmacokinetics



- Pharmacokinetic/pharmacodynamic modeling predicted emicizumab concentration  $\geq 45$  µg/mL would result in  $>50\%$  of patients achieving zero bleeds
- Target met with weekly subcutaneous dosing: mean trough plasma concentrations  $>50$  µg/mL achieved and sustained once steady-state was reached

# HAVEN 1 safety summary

## All emicizumab patients

	Total (N=103)
Total number of adverse events (AEs), n	198
Total patients $\geq 1$ AE, n (%)	73 (70.9)
Serious AE*	9 ( 8.7)
Thrombotic microangiopathy (TMA)**	3 ( 2.9)
Thrombotic event	2 ( 1.9)
Death**	1 (<1)
AEs leading to withdrawal	2 ( 1.9)
Grade $\geq 3$ AE	8 ( 7.8)
Related AE	23 (22.3)
Local injection-site reaction	15 (14.6)

- \*\*Third TMA event occurred after primary data cut-off; patient also experienced fatal rectal hemorrhage
- Thrombotic events were skin necrosis/superficial thrombophlebitis in one patient, and cavernous sinus thrombosis in a second patient
- No patients tested positive for anti-drug antibodies

\*Additional serious AEs included one event each of: iron deficiency anemia, sepsis, hemarthrosis, muscle hemorrhage, gastric ulcer hemorrhage, headache and hematuria. Two additional withdrawals not related to AEs; one withdrawal by patient, one withdrawal due to physician decision.

# HAVEN 1

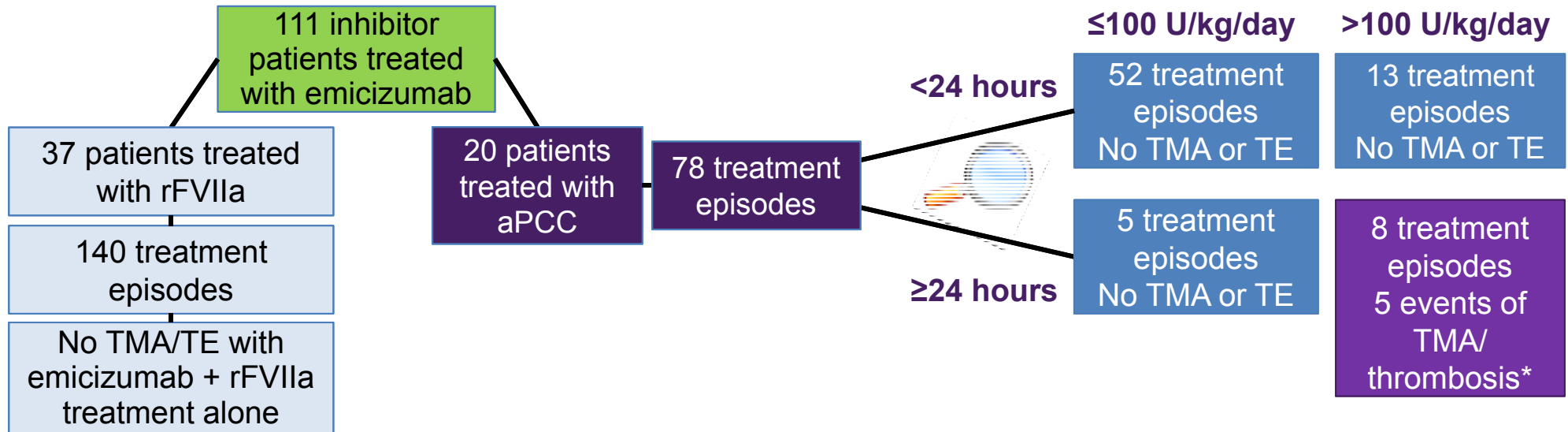
## Characteristics of TMA and thrombotic events

Event	Received BPA prior to event?	Anti-coagulation	Resolution	Additional treatment	Restarted emicizumab
Thrombosis #1	aPCC	No	Resolved	Supportive care only	Yes
Thrombosis #2	aPCC	No	Resolving	Supportive care only	No
TMA #1	aPCC/rFVIIa	N/A	Resolved	Plasmapheresis	No
TMA #2	aPCC	N/A	Resolved	Supportive care only	Yes
TMA #3	aPCC/rFVIIa	N/A	Resolving*	Plasmapheresis	No

- Commonality among all cases was high cumulative doses of aPCC over multiple days prior to event and improvement shortly after discontinuing aPCC
- TMA events in two patients were short-lived; resolved soon after aPCC treatment was stopped
  - rFVIIa treatment in TMA #1 included treatment during resolution of the event
- \*Patient treated for rectal hemorrhage, which was eventually fatal; death was deemed unrelated to 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.

- Once-weekly emicizumab prophylaxis administered subcutaneously successfully prevented or reduced bleeds in PwHA with inhibitors
  - Reduction in bleed rate of 87% vs no prophylaxis
  - Reduction in bleed rate of 79% vs prior prophylactic BPAs
  - 63% of patients randomized to emicizumab prophylaxis and 71% of patients previously on BPA prophylaxis experienced zero bleeds
- Substantial reduction in bleeds was associated with statistically significant, clinically meaningful benefits in HRQoL and health status



- Risk of TE and TMA events seen with aPCC administered with emicizumab prophylaxis may be mitigated with BPA treatment guidance
  - Serious thrombotic and TMA events were seen when aPCC was administered at repeated doses (>100 U/kg/day on average for ≥24 hours) to treat breakthrough bleeds during emicizumab prophylaxis
  - No serious TE or TMA events occurred with emicizumab alone or when rFVIIa alone was used for breakthrough bleed treatment
  - aPCC should be avoided if possible in patients receiving emicizumab
    - If necessary to use, lower doses are indicated and caution should be used

# HAVEN 1 conclusions (3)

Download this presentation: <http://tago.ca/H1PrD>

- Results represent a potential paradigm shift and new standard of care for treatment of hemophilia A with inhibitors, with an effective weekly, subcutaneous, prophylactic therapeutic option
- Data from this study have been submitted for approval consideration to the EMA and the US FDA

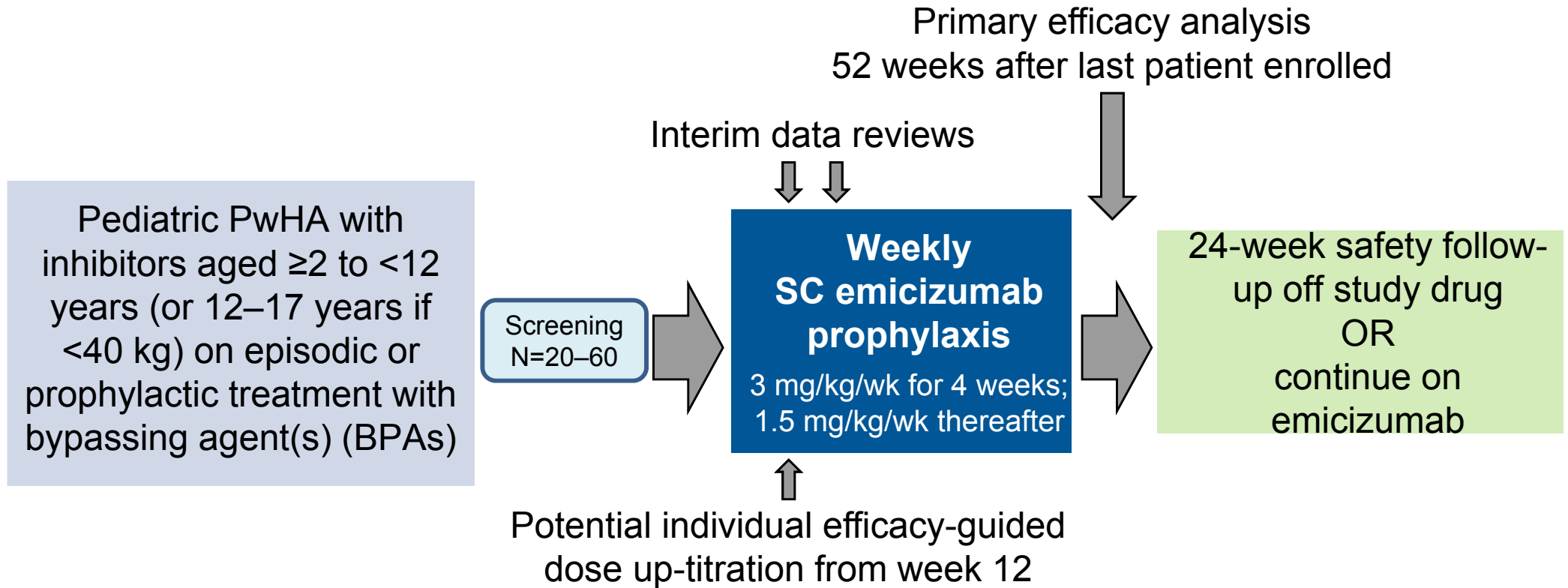
# **HAVEN 2: Efficacy, safety and pharmacokinetics of once-weekly prophylactic emicizumab (ACE910) in pediatric patients (<12 years) with hemophilia A with inhibitors: interim analysis of single-arm, multicenter, open-label, phase 3 study**

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Maria Elisa Mancuso<sup>5</sup>, Tiffany Chang<sup>6</sup>, Marianne Uguen<sup>7</sup>,  
Christophe Dhalluin<sup>7</sup>, Christophe Schmitt<sup>7</sup>, Sabine Fuerst-Recktenwald<sup>7</sup>,  
Midori Shima<sup>8</sup>, Rebecca Kruse-Jarres<sup>9</sup>**

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# HAVEN 2 study design

## Once-weekly subcutaneous emicizumab prophylaxis



NCT02795767.

Patients from non-interventional study (NCT02476942) (Cohort B) permitted to enroll.

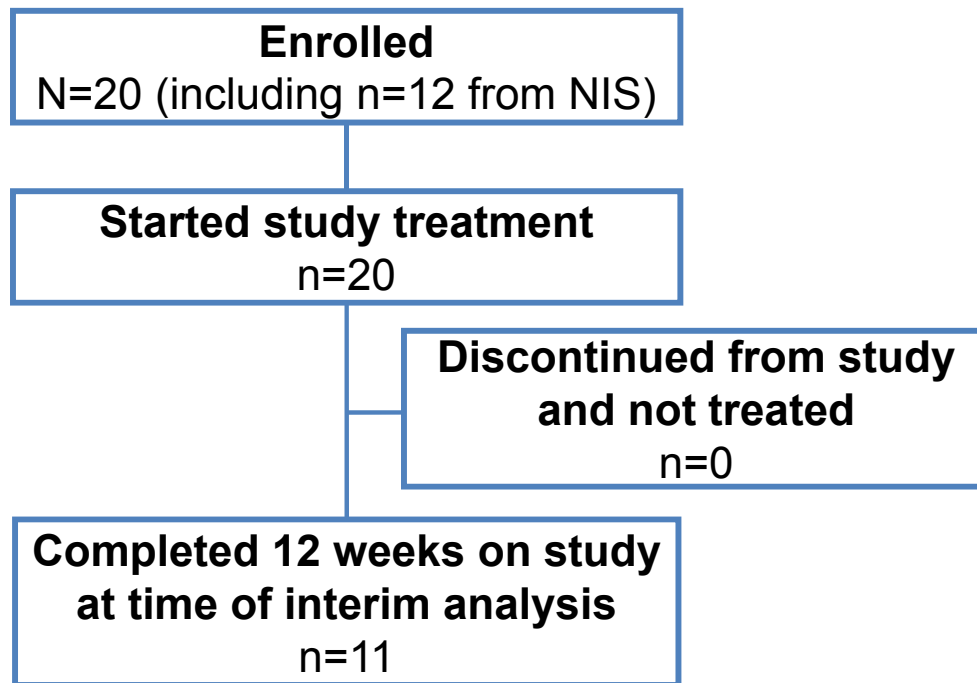
First interim review – starting maintenance dose evaluated after 3–5 patients dosed for ≥12 weeks.

Second interim review – once ≥10 patients dosed for ≥12 weeks.

SC, subcutaneous.

# HAVEN 2

## Patient disposition



- No dose up-titrations
- Efficacy analyses include only patients aged <12 years (n=19)
  - Summary statistics on efficacy include patients with  $\geq 12$  weeks on study (n=10)
  - Intra-individual comparison includes only those who also participated in the NIS (n=8)
- Safety analyses include all treated patients (n=20)

# HAVEN 2

## Demographics and baseline characteristics

	Emicizumab 1.5 mg/kg QW (N=20)		Emicizumab 1.5 mg/kg QW (N=20)
<b>Sex, male, n (%)</b>	20 (100.0)	<b>Treatment, n (%)</b>	
<b>Age</b>		Episodic	2 (10.0)
Median (min–max), years	8.5 (3–12)	Prophylactic	18 (90.0)
2 to <6 years, n (%)	4 (20.0)	<b>Weight (kg), median (min–max)</b>	26.9 (14.2–63.0)
6 to <12 years, n (%)	15 (75.0)	<b>Bleeds prior 24 weeks, median (min–max)</b>	6.0 (0–35)
≥12 years, n (%)	1 (5.0)	<b>Target joints, n (%)</b>	
<b>Hemophilia severity, n (%)</b>		No	15 (75.0)
Mild <sup>†</sup>	1 (5.0)	Yes	5 (25.0)
Severe	19 (95.0)	1	2 (40.0)
<b>Previous ITI, n (%)</b>		>1	3 (60.0)
Yes	17 (85.0)		
No	3 (15.0)		

<40 kg body weight if ≥12 years.

Patient with mild disease at baseline had severe disease at study entry..

# HAVEN 2

## Bleed-related endpoints

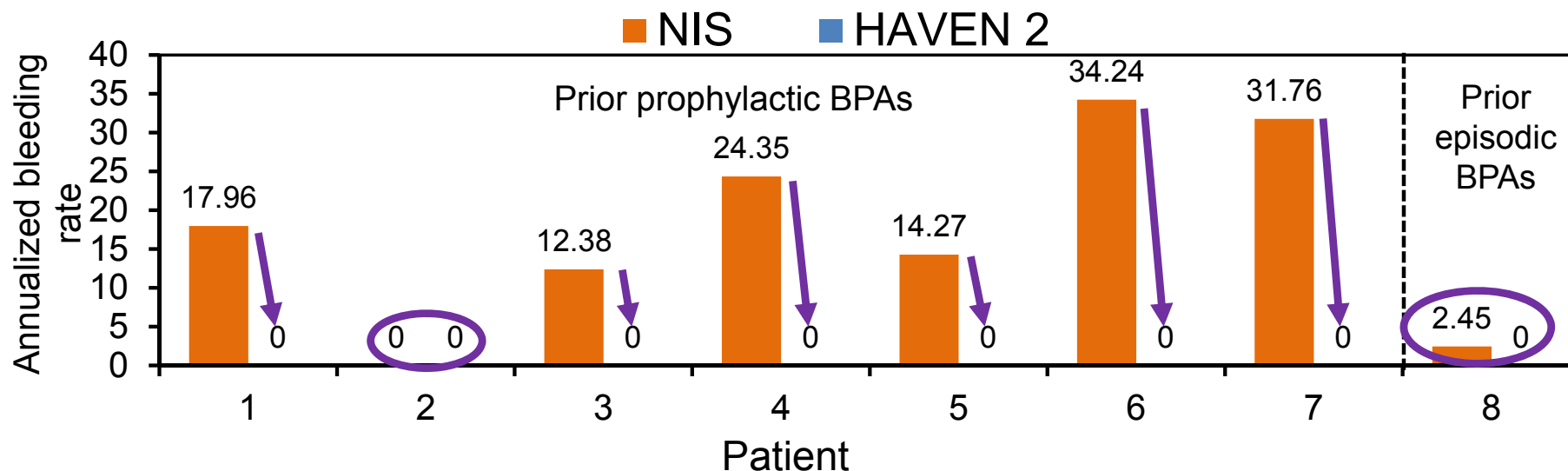
Endpoint	Mean ABR (95% CI) N=10	% zero bleeds (95% CI) N=19
Treated bleeds	<b>0.4</b> (0.00; 4.51)	<b>94.7</b> (74.0; 99.9)
All bleeds	<b>3.7</b> (0.94; 9.81)	<b>63.2</b> (38.4; 83.7)
Treated spontaneous bleeds	<b>0.4</b> (0.00; 4.51)	<b>94.7</b> (74.0; 99.9)
Treated joint bleeds	<b>0.0</b> (NA; 3.69)	<b>100</b> (82.4; 100.0)
Treated target joint bleeds	<b>0.0</b> (NA; 3.69)	<b>100</b> (82.4; 100.0)

- Median (range) observation time for 19 patients aged <12 years, 12.1 (7–14) weeks
- In total, 14 bleeds reported in 7 patients
  - Only 1 was treated – spontaneous bleed
  - None occurred in a joint or muscle

Majority of patients receiving emicizumab prophylaxis reported zero bleeds

# 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
122	99	61	99	118	89	120	86	128	85	128	85	138	85	149	99

Follow-up (days)  
(NIS/HAVEN 2)

- Intra-individual comparison performed for 8 NIS patients on HAVEN 2 study  $\geq 12$  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



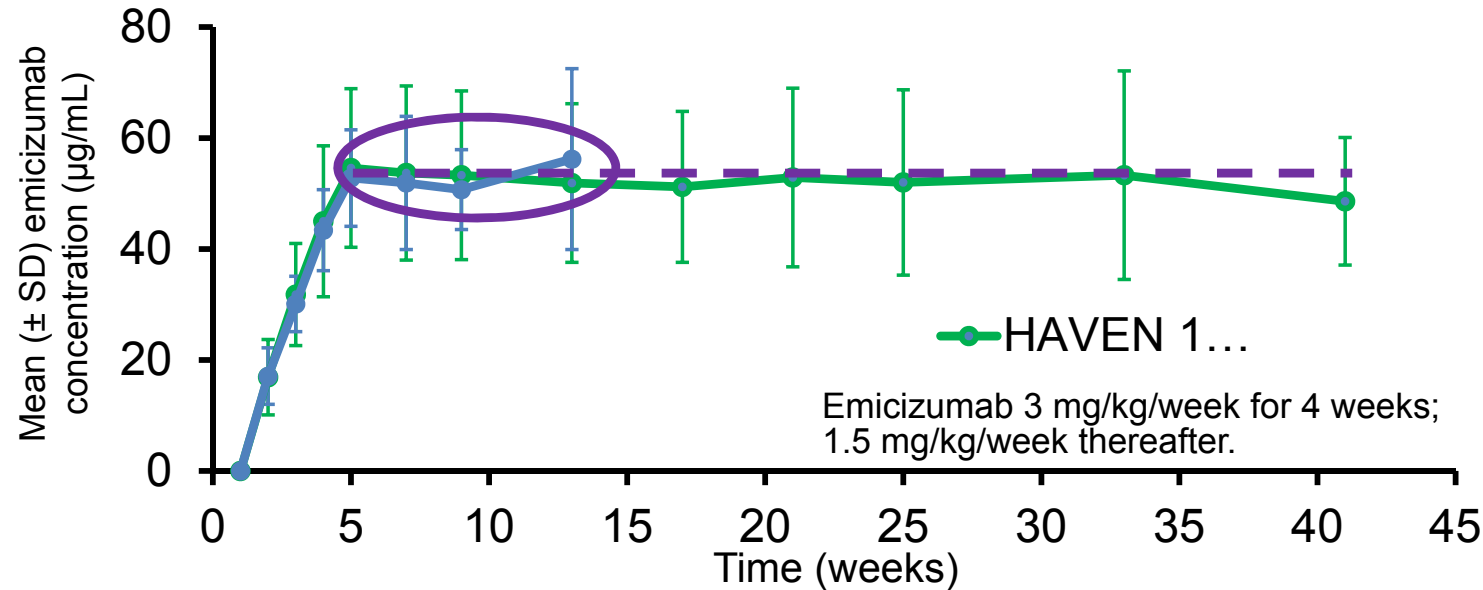
# HAVEN 2 safety summary

Adverse events, n (%)	Emicizumab 1.5 mg/kg QW (N=20)
<b>Total number of AEs</b>	43
<b>Total patients experiencing <math>\geq 1</math> AE, n (%)</b>	14 (70.0)
Serious AE	3 (15.0)
Grade $\geq 3$ AE	3 (15.0)
<b>Related AE</b>	<b>3 (15.0)</b>
Local injection-site reaction	3 (15.0)

- Serious AEs: mouth hemorrhage, appendicitis, catheter-site infection
- **All related AEs were mild injection-site reactions (3 patients; 9 events)**
- No thromboembolic or thrombotic microangiopathy events observed
- No patients tested positive for anti-drug antibodies

# HAVEN 2

## Emicizumab pharmacokinetics



- Target emicizumab exposure was  $\geq 45 \mu\text{g/mL}$
- Emicizumab PK profile comparable with that seen in adolescent/adult PwHA
- With weekly subcutaneous dosing, mean trough emicizumab plasma concentrations  $> 50 \mu\text{g/mL}$  were achieved and sustained once at steady-state

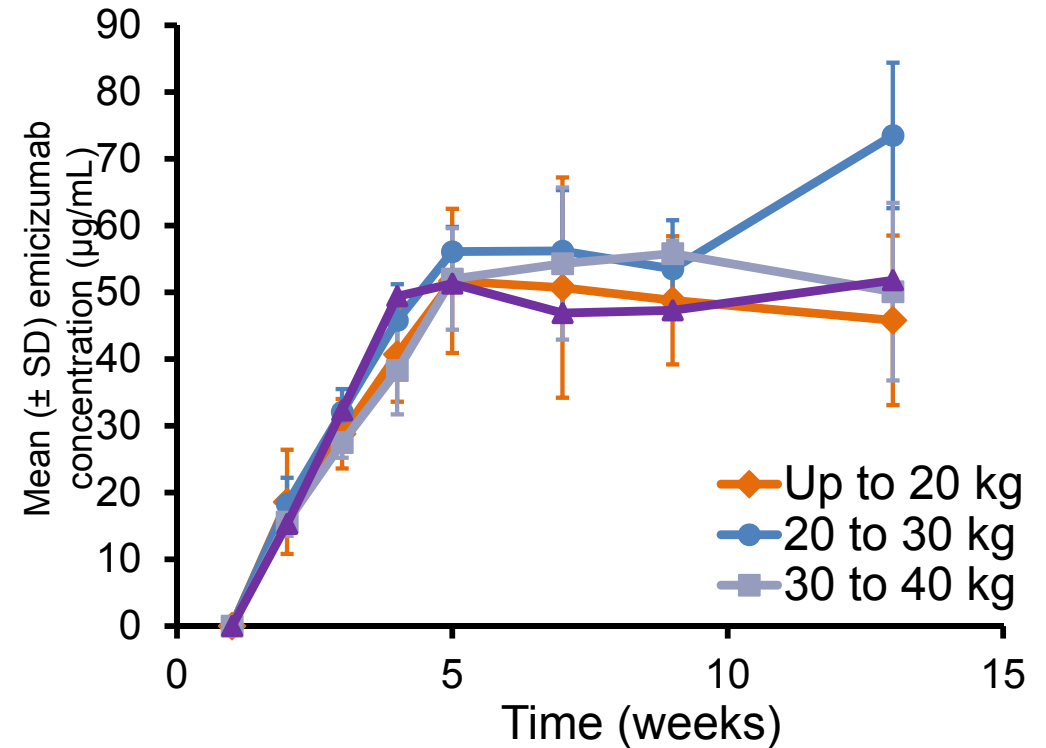
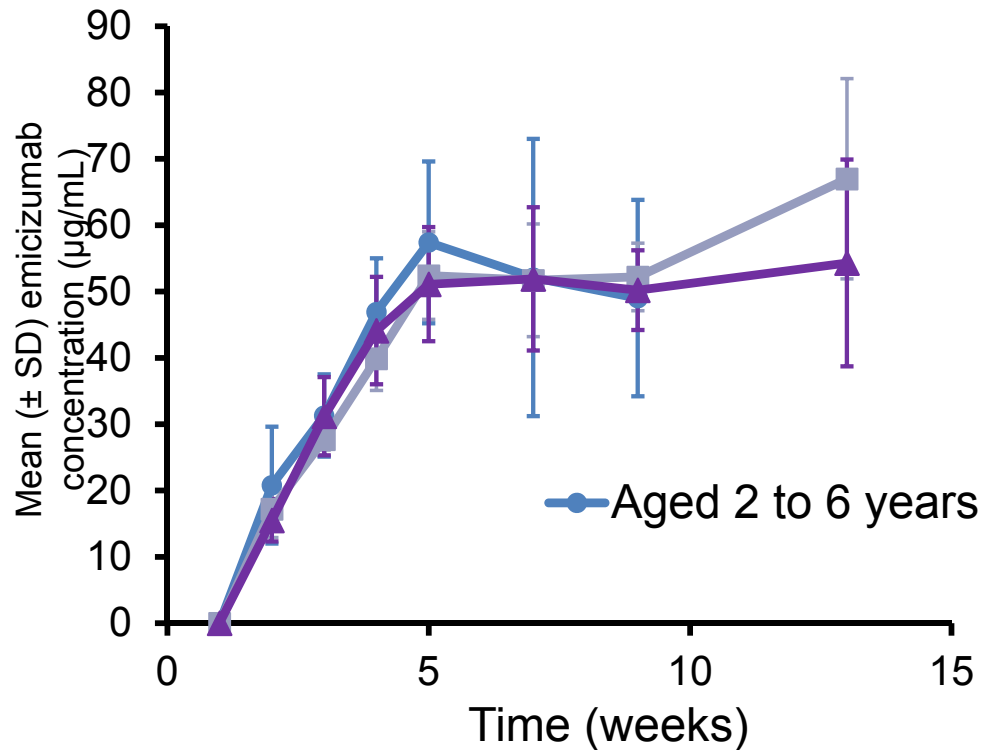
SD, standard deviation.

Yoneyama K, et al. *Clin Pharmacol Ther* 2016;99 Suppl 1:S33.

Oldenburg J, et al. ISTH 2017; abstract ASY 01.1.

# HAVEN 2

## Emicizumab pharmacokinetics by age group and body weight



- Mean trough emicizumab concentrations in plasma were consistent across age groups and body weight

## HAVEN 2 conclusions (1)

- At 12-week follow-up, efficacy results are promising and clinically meaningful in pediatric PwHA with inhibitors
  - Emicizumab successfully prevented or reduced bleeds
  - Clinically meaningful reductions in annualized bleeding rate shown with emicizumab versus prior regimen (from non-interventional study)
- Safety profile of emicizumab was favorable and well tolerated, with no thromboembolic or thrombotic microangiopathy events reported
- Target exposure was achieved at 50 µg/mL in pediatric population (>2 years of age), with PK profile consistent with adolescent/adult population
  - Pediatric dose confirmed to be the same as adult dose

## HAVEN 2 conclusions (2)

- Emicizumab has the potential to provide a paradigm shift in the treatment of pediatric PwHA with inhibitors, with an effective weekly, subcutaneous therapeutic option
- Study continues with a total of 62 patients enrolled, including 4 patients <2 years of age; patients will be followed  $\geq 52$  weeks
- Data from this study have been submitted for approval consideration to the EMA and the US FDA

## 将来見通し

すべての革新は患者さんのために



Roche ロシュ グループ

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