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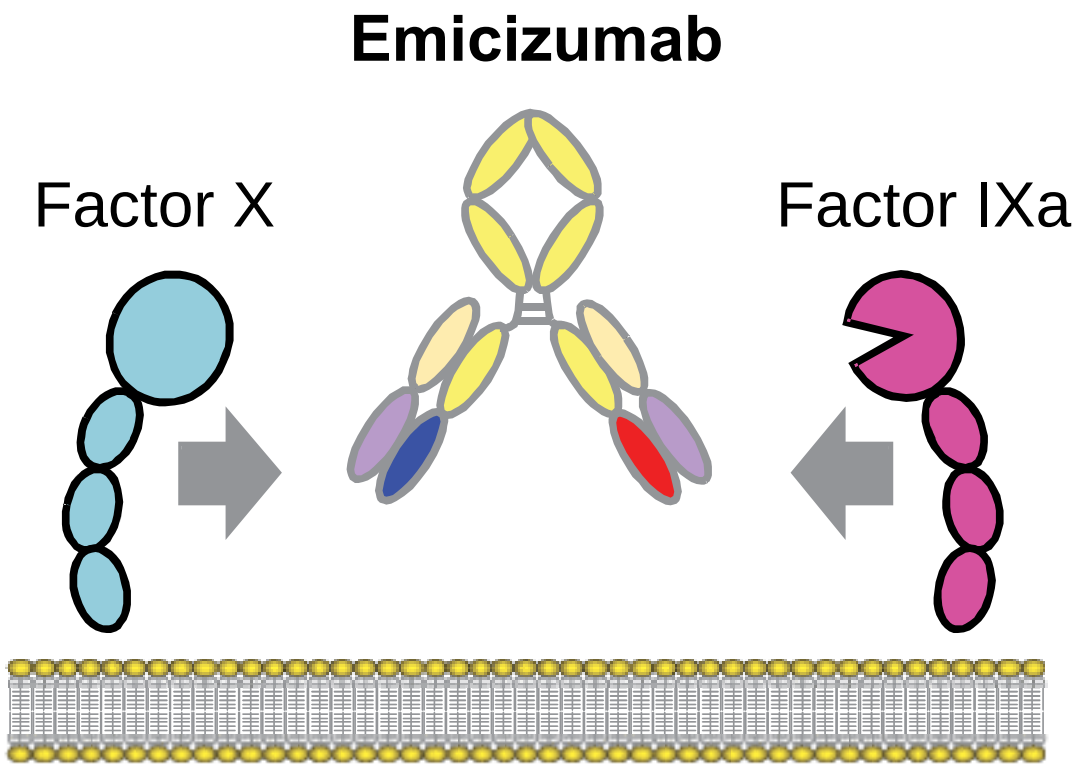
*Emicizumab is an investigational product and is not approved or licensed for the treatment of patients with hemophilia A or any other medical condition*

# Disclosures

Received grants and personal fees and served as member on a Board of Directors or Advisory Committee for Baxter, Bayer, Biogen Idec, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Shire and Sobi.

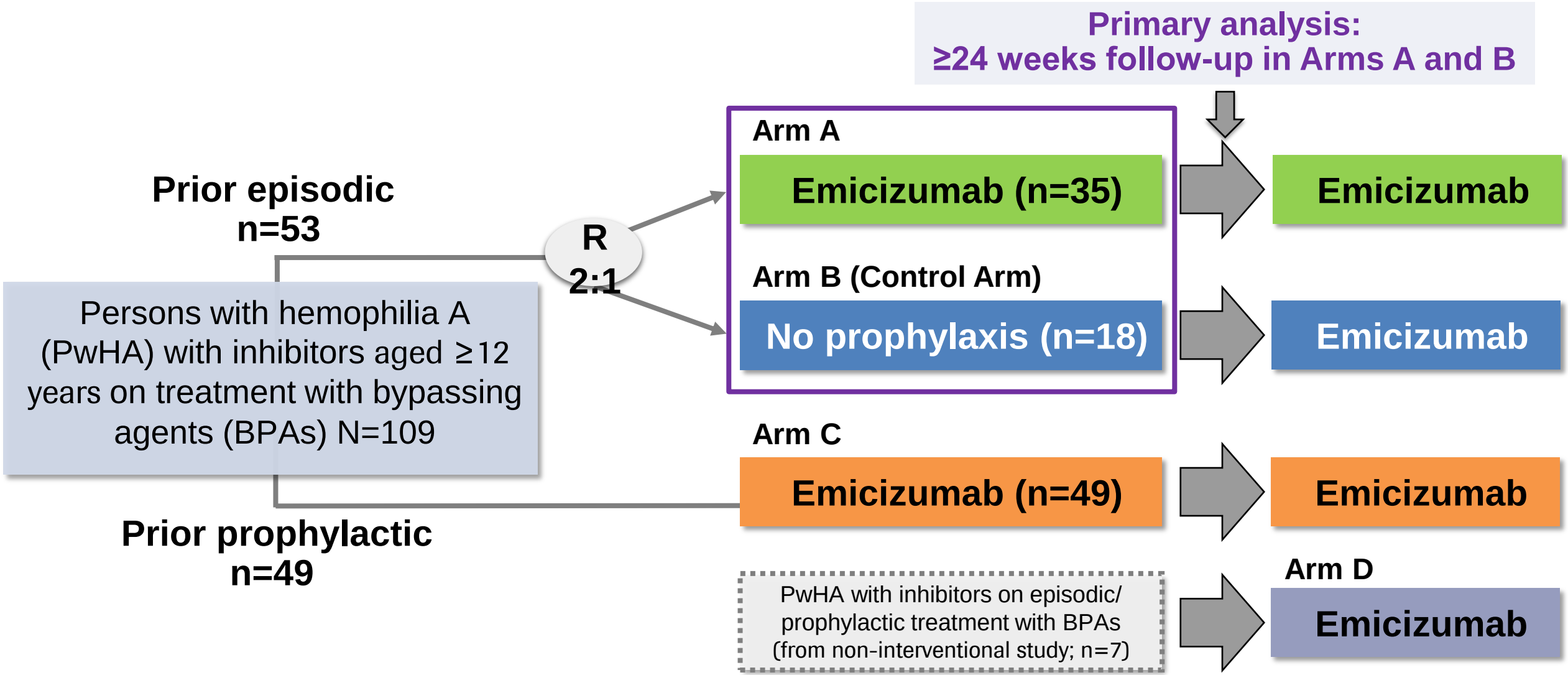
# Emicizumab (ACE910)
## Humanized bispecific monoclonal antibody




- 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

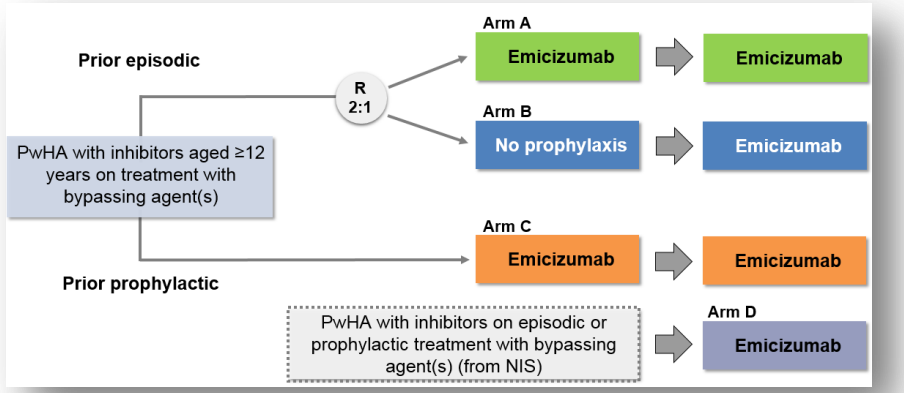
Kitazawa T, et al. *Nat Med* 2012;18:1570–4.
Sampei Z, et al. PLoS One 2013;8:e57479.
Uchida N, et al. *Blood* 2016;127:1633–41.
Shima S, et al. *N Engl J Med* 2016;374:2044–53.

# HAVEN 1 study design
## Once-weekly subcutaneous emicizumab prophylaxis




NCT02622321: phase 3, open-label, multicenter, randomized study.
Emicizumab 3 mg/kg/week for 4 weeks; 1.5 mg/kg/week thereafter.
Arm D: Patients unable to enroll into Arms A, B or C before they closed to enrollment.

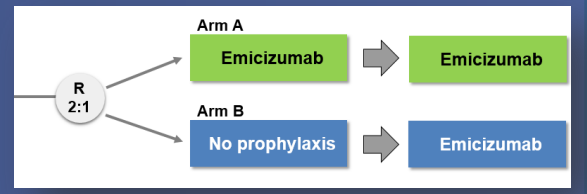
# HAVEN 1
## Demographics/baseline disease characteristics

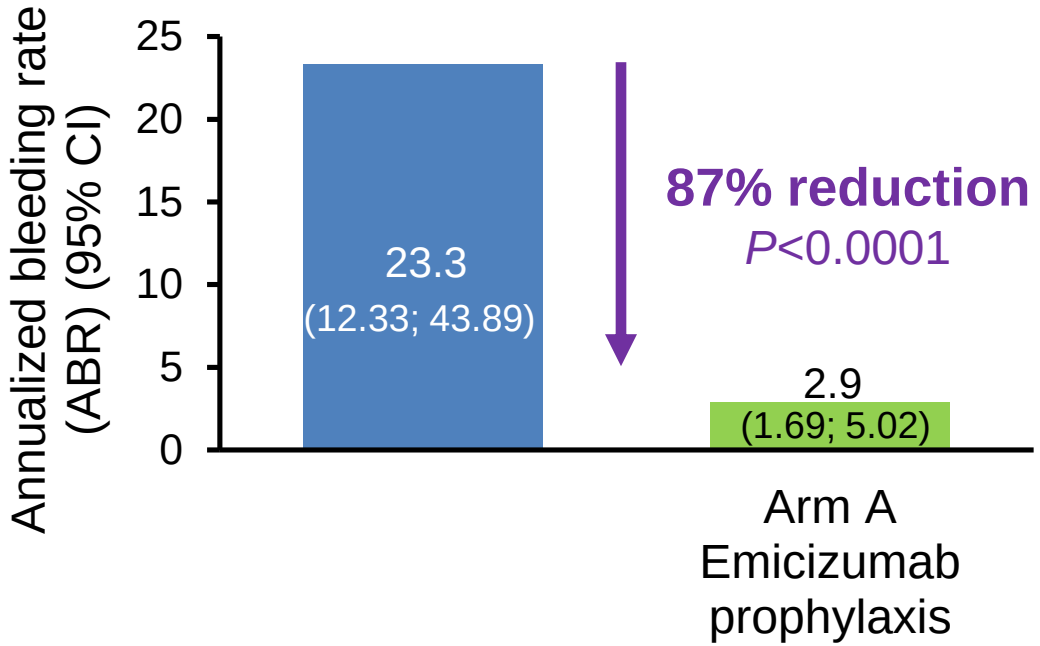



| | Arm A: Emicizumab prophylaxis (prior episodic BPAs) n=35 | Arm B: No prophylaxis (prior episodic BPAs; control arm) n=18 | Arm C: Emicizumab prophylaxis (prior BPA prophylaxis) n=49 | Arm D: Emicizumab prophylaxis (prior BPAs; episodic or prophylactic) n=7 | Total N=109 |
|---|---|---|---|---|---|
| **Age** | | | | | |
| 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) |
| **Bleeds in 24 weeks prior to study entry, n (%)** | | | | | |
| ≥9 | 24 (68.6) | 13 (72.2) | 26 (53.1) | 3 (42.9) | 66 (60.6) |
| **Target joints, n (%)** | | | | | |
| 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) |
| **Highest historical inhibitor titer (BU)** | | | | | |
| 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 |
| **Previously treated with ITI, n (%)** | 14 (40.0) | 7 (38.9) | 33 (67.3) | 3 (42.9) | 57 (52.3) |

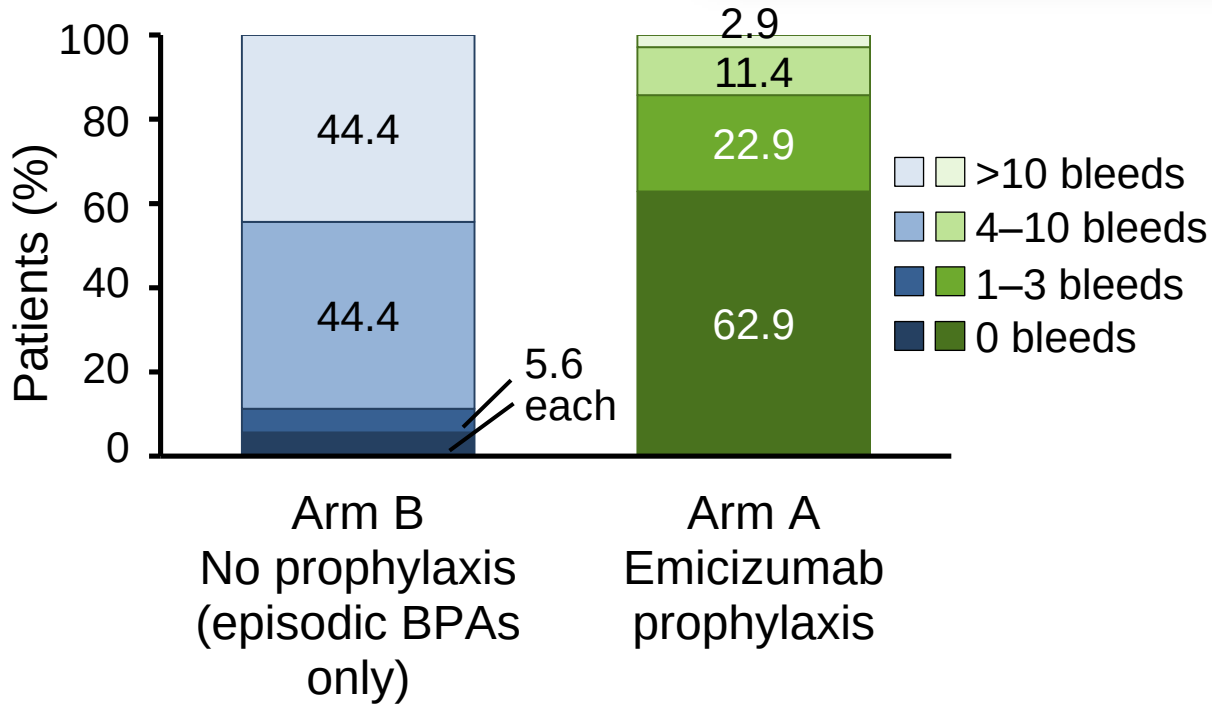
BU, Bethesda units; ITI, immune tolerance induction.

# HAVEN 1 primary endpoint
## Randomized comparison of treated bleeds




| | | |
|---|---|---|
| Median ABR (IQR) | **18.8** (12.97; 35.08) | **0.0** (0.00; 3.73) |




- 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

ABR calculated with negative binomial regression model.
Median ABR calculated by number of bleeds/duration of efficacy period in days*365.25.
CI, confidence interval; IQR, interquartile range.

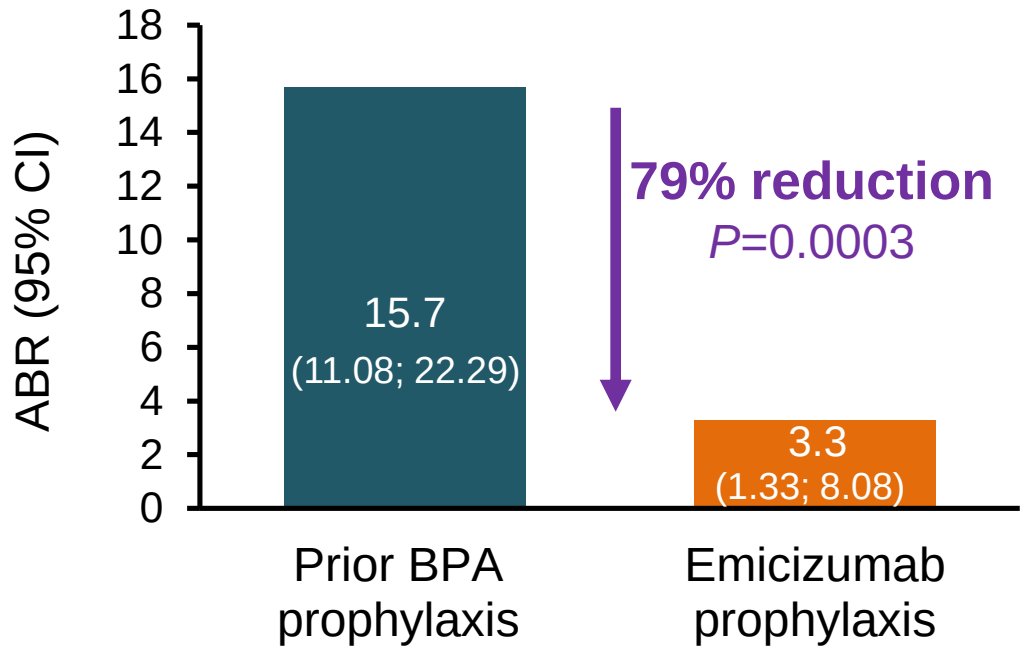
Primary analysis data cutoff – October 25, 2016

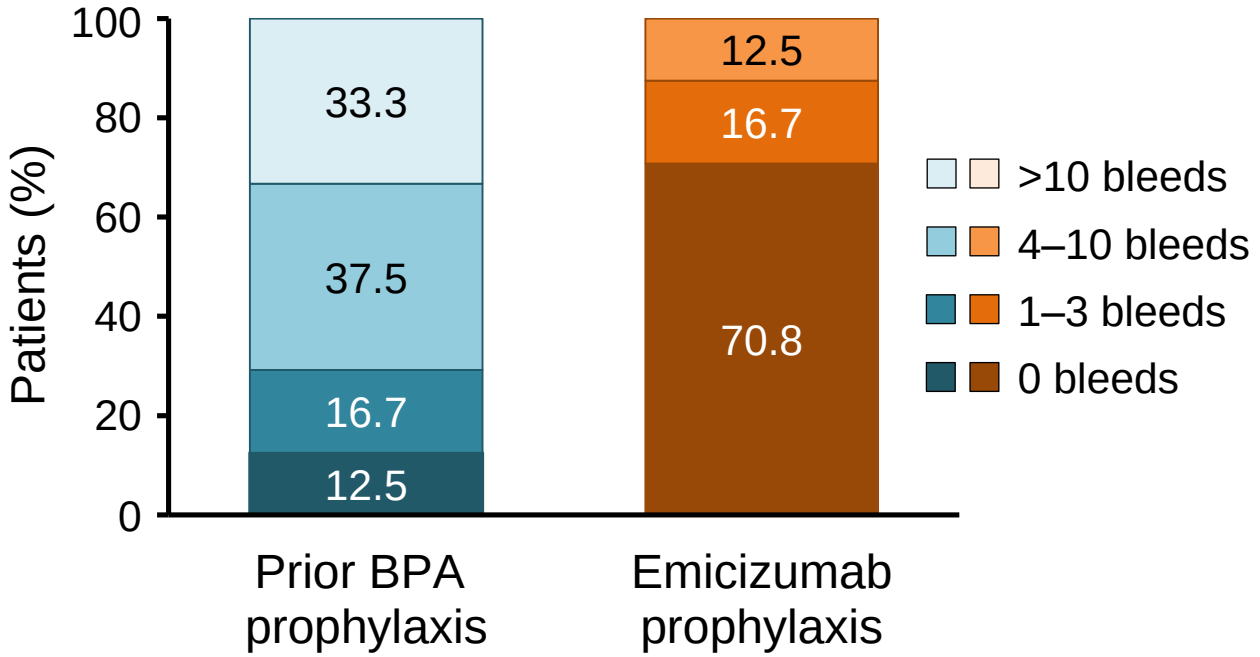
# HAVEN 1 secondary bleed-related endpoints
## Consistent statistically significant reductions in ABR

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

ABR calculated using negative binomial regression model.
RR, risk ratio.

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


| | | |
|---|---|---|
| Median ABR (IQR) | **12.0** (5.73; 24.22) | **0.0** (0.00; 2.23) |

- 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

ABR calculated with negative binomial regression model.
Median ABR calculated by number of bleeds/duration of efficacy period in days*365.25.

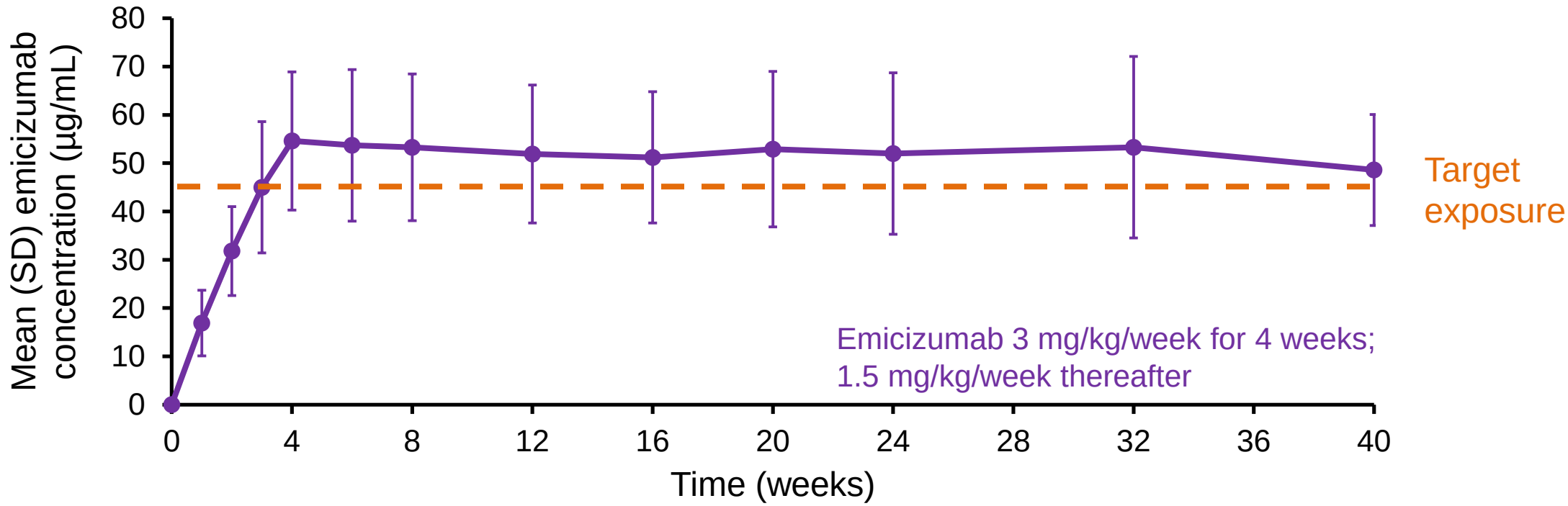
# HAVEN 1 health-related quality of life and health status
## Randomized comparison

| Measure | Number of patients (Arm B/Arm A) | Clinically meaningful difference | Difference in adjusted means (95% CI) (Arm B vs Arm A) | *P*-value |
|---|---|---|---|---|
| **Haem-A-QoL** (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 |
| **EQ-5D-5L** | | | | |
| 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

Wyrwich KW, et al. *Haemophilia* 2015;21:578–84.
Walters SJ, et al. *Qual Life Res* 2005;14:1523–32.
Pickard AS, et al. *Health Qual Life Outcomes* 2007;5:70.

# HAVEN 1
## Emicizumab pharmacokinetics




- Pharmacokinetic/pharmacodynamic modeling predicted emicizumab concentration ≥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

SD, standard deviation.
Yoneyama K, et al. *Clin Pharm Ther* 2016;99(suppl 1):S33.

# HAVEN 1 safety summary
## All emicizumab patients

| | Total (N=103) |
|---|---|
| **Total number of adverse events (AEs), n** | 198 |
| **Total patients ≥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 ≥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.

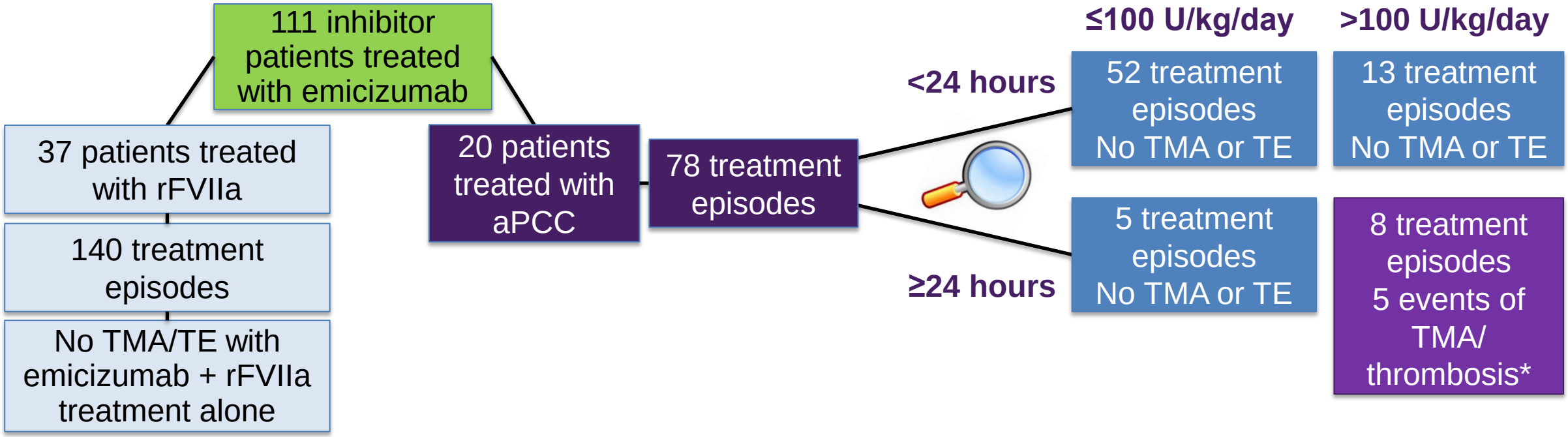
# HAVEN 1
# Characteristics of TMA and thrombotic events

| 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

aPCC, activated prothrombin complex concentrate; rFVIIa, activated recombinant FVII.

# HAVEN 1 updated data
# Assessment of interaction between emicizumab and aPCC




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

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

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

# HAVEN 1 conclusions (1)

- 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

# HAVEN 1 conclusions (2)

- 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)

- 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

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  - Study participants and their families
  - Study investigators and site personnel:

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# HAVEN 1 data now published in NEJM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Emicizumab Prophylaxis in Hemophilia A with Inhibitors

Johannes Oldenburg, M.D., Ph.D., Johnny N. Mahlangu, M.D., Benjamin Kim, M.D., Christophe Schmitt, Pharm.D., Michael U. Callaghan, M.D., Guy Young, M.D., Elena Santagostino, M.D., Ph.D., Rebecca Kruse-Jarres, M.D., M.P.H., Claude Negrier, M.D., Ph.D., Craig Kessler, M.D., Nancy Valente, M.D., Elina Asikanius, M.Sc., Gallia G. Levy, M.D., Ph.D., Jerzy Windyga, M.D., and Midori Shima, M.D., Ph.D.

**Available at [http://www.nejm.org](http://www.nejm.org)**

# Thank you

# 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

**Guy Young[1], Johannes Oldenburg[2], Ri Liesner[3], Victor Jiménez-Yuste[4], Maria Elisa Mancuso[5], Tiffany Chang[6], Marianne Uguen[7], Christophe Dhalluin[7], Christophe Schmitt[7], Sabine Fuerst-Recktenwald[7], Midori Shima[8], Rebecca Kruse-Jarres[9]**

[1]Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA, USA; [2]Universitätsklinikum Bonn, Bonn Germany; [3]North London Paediatric Haemophilia Network, London, UK; [4]University Hospital La Paz, Madrid, Spain; [5]Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy; [6]Genentech Inc., South San Francisco, CA, USA; [7]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [8]Department of Pediatrics, Nara Medical University, Kashihara, Nara, Japan; [9]Bloodworks Northwest, Seattle, WA, USA

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# Disclosures

Received honoraria and/or consulting fees from Alnylam, Bayer, Biogen Idec, Kedrion, Novo Nordisk, Roche, and Shire.

# Current standard of care and unmet medical needs for children with hemophilia A with inhibitors

- Exposure to factor VIII (FVIII) concentrate leads to development of neutralizing anti-FVIII alloantibodies (inhibitors) in ~30% of persons with hemophilia A (PwHA)
  - Substantial increase in morbidity and decreased health-related quality of life (HRQoL)
- Treatment for PwHA with inhibitors
  - Immune tolerance induction or treatment with bypassing agents
  - Frequent intravenous infusions often require long-term use of central venous access devices (CVADs) for pediatric PwHA
- Unmet medical needs for PwHA with inhibitors
  - Suboptimal efficacy with bypassing agents vs FVIII for patients without inhibitors
  - High treatment burden and impaired HRQoL

Witmer C and Young G. *Ther Adv Hematol* 2013;4:59–72.
Morfini M, et al. *Haemophilia* 2008;14 Suppl 6:20–2.
Gringeri A, et al. *Blood* 2003;102:2358–63.
Monahan PE, et al. *Am J Prev Med* 2011;41:S360–8.
Astermark J. *Semin Hematol* 2006;43(suppl 4):S3–S7.
Santagostino E and Mancuso ME. *Haemophilia* 2010;16(suppl 1):20–4.
Gringeri A, et al. *Haemophilia* 2013;19:736–43.
Shapiro AD and Hedner U. *Ther Adv Drug Saf* 2011;2:213–25.

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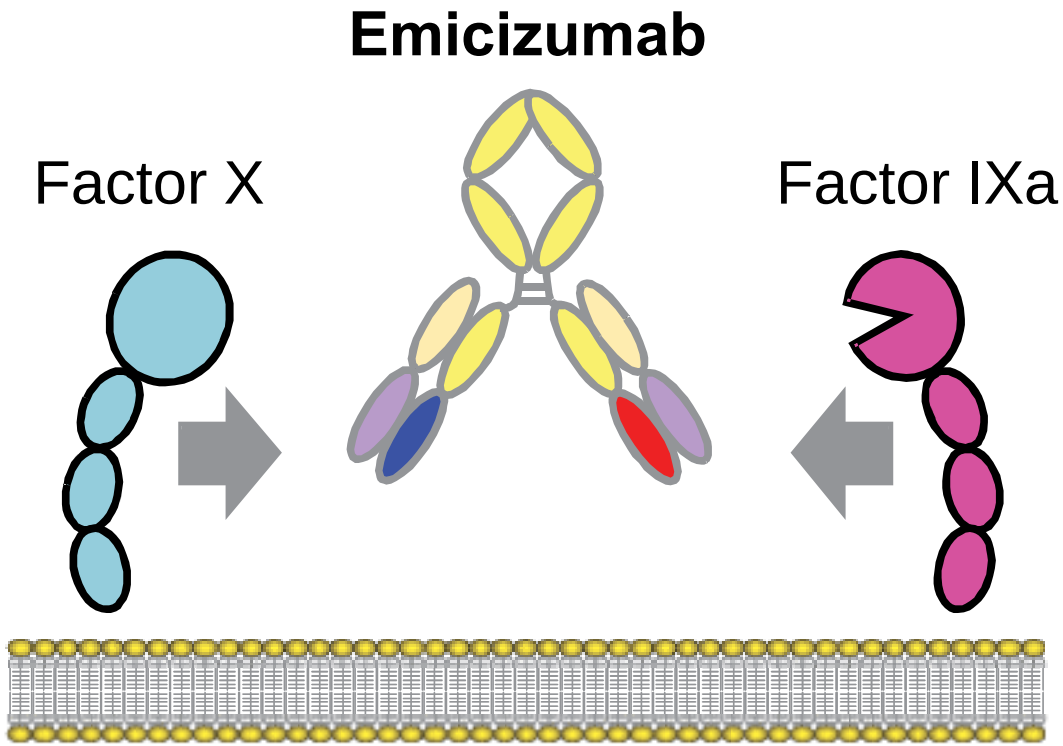
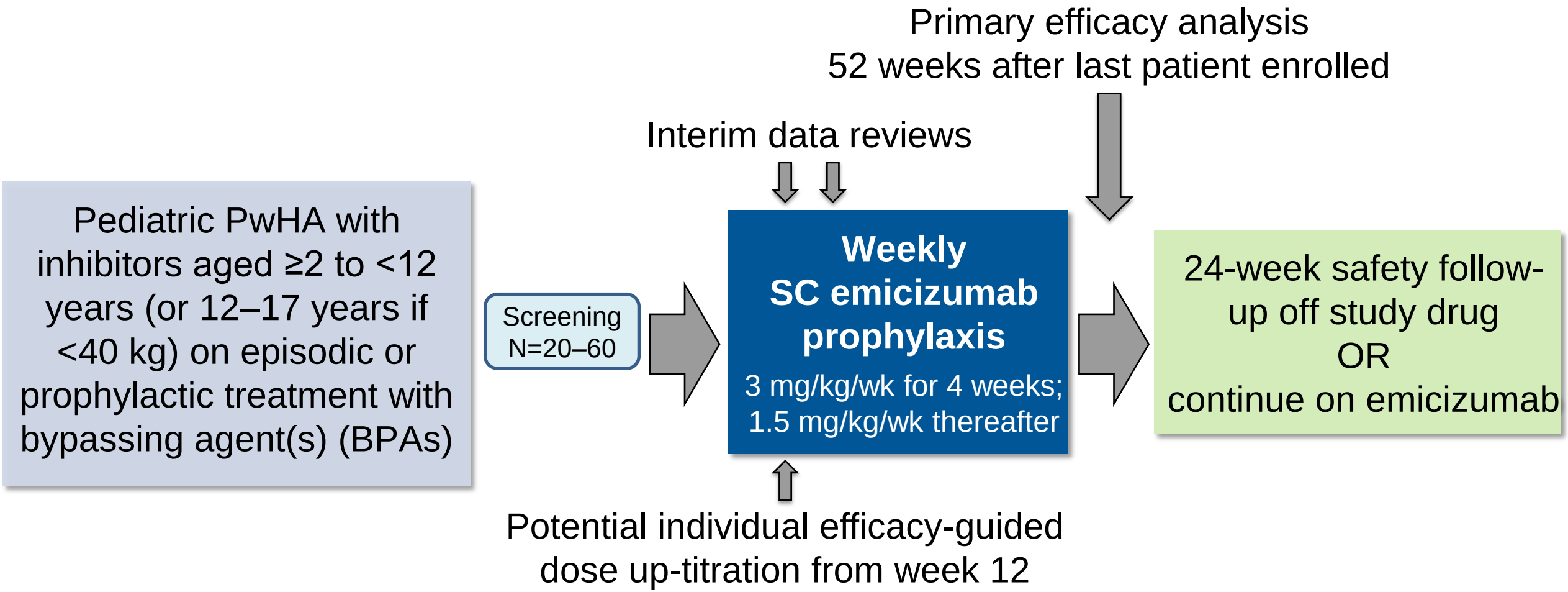
## Humanized bispecific monoclonal antibody




- Novel humanized bispecific monoclonal antibody
- Bridges activated FIX and FX to restore function of missing activated FVIII
- No structural homology to FVIII – not expected to induce FVIII inhibitors or be affected by presence of inhibitors
- Administered subcutaneously once weekly

Kitazawa T, et al. *Nat Med* 2012;18:1570-4.
Sampei Z, et al. PLoS One 2013;8:e57479.
Uchida N, et al. *Blood* 2016;127:1633-41.
Shima S, et al. *N Engl J Med* 2016;374:2044-53.

# HAVEN 2 study design
## Once-weekly subcutaneous emicizumab prophylaxis

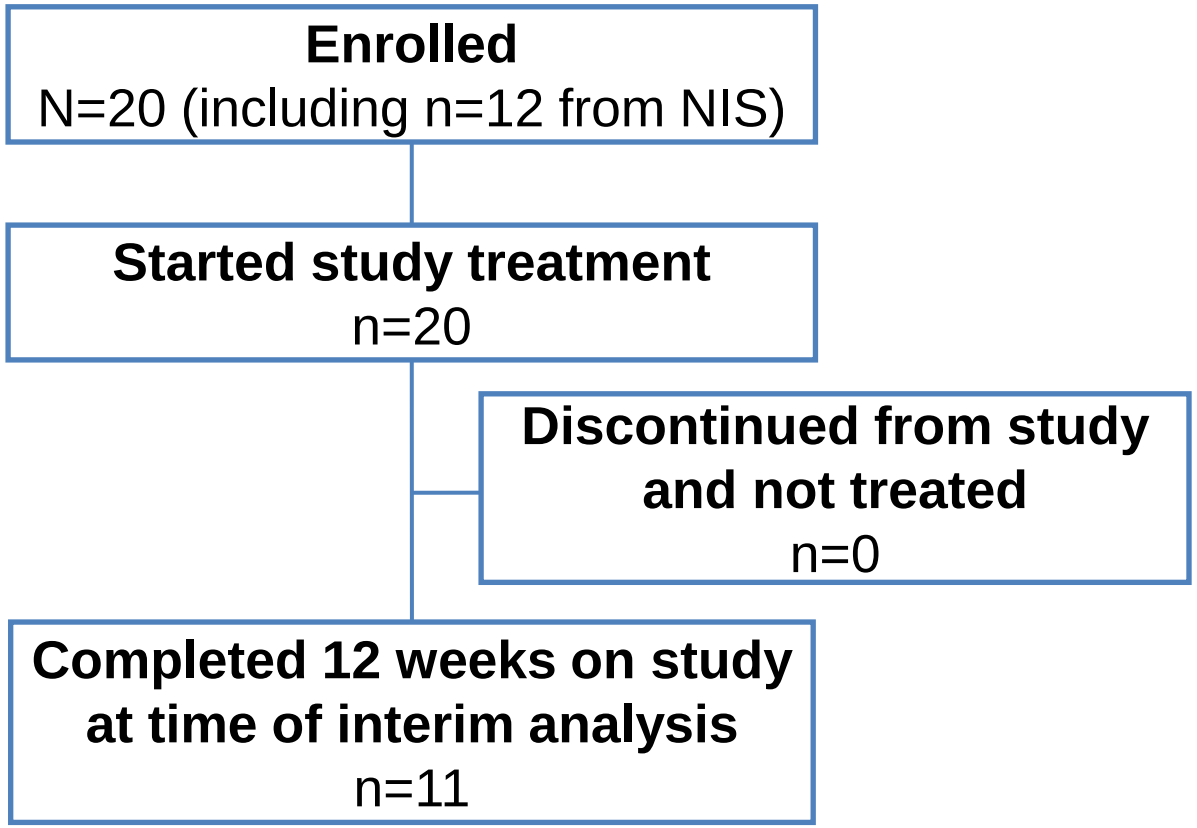



NCT02795767.
Patients from non-interventional study (NCT02476942) (Cohort B) permitted to enroll.
First interim review – starting maintenance dose evaluated after 3–5 patients dosed for ≥12 weeks.
Second interim review – once ≥10 patients dosed for ≥12 weeks.
SC, subcutaneous.

# HAVEN 2
## Study objectives

- Phase 3, single-arm, open-label, multicenter study to assess descriptively efficacy, safety, and PK of once-weekly SC emicizumab prophylaxis in pediatric PwHA with inhibitors previously receiving BPA treatment
- Efficacy objectives
  - Clinical effect of emicizumab prophylaxis on bleed rate
  - Bleed rate with emicizumab prophylaxis versus historical bleed rate (intra-individual comparison for those who previously participated in non-interventional study)
- Safety objectives
  - Incidence of AEs, including serious AEs, AEs leading to drug discontinuation, and clinical lab abnormalities
  - Incidence of anti-emicizumab antibodies
- PK objectives
  - Characterize emicizumab exposure ($C_{trough}$)

# 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 ≥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)

NIS, non-interventional study (NCT02476942).

# HAVEN 2
## Demographics and baseline characteristics

| | Emicizumab 1.5 mg/kg QW (N=20) |
|---|---|
| **Sex, male, n (%)** | 20 (100.0) |
| **Age** | |
| Median (min–max), years | 8.5 (3–12) |
| 2 to <6 years, n (%) | 4 (20.0) |
| 6 to <12 years, n (%) | 15 (75.0) |
| ≥12 years, n (%) | 1 ( 5.0) |
| **Hemophilia severity, n (%)** | |
| Mild† | 1 (5.0) |
| Severe | 19 (95.0) |
| **Previous ITI, n (%)** | |
| Yes | 17 (85.0) |
| No | 3 (15.0) |

| | Emicizumab 1.5 mg/kg QW (N=20) |
|---|---|
| **Treatment, n (%)** | |
| Episodic | 2 (10.0) |
| Prophylactic | 18 (90.0) |
| **Weight (kg), median (min–max)** | 26.9 (14.2–63.0) |
| **Bleeds prior 24 weeks, median (min–max)** | 6.0 (0–35) |
| **Target joints, n (%)** | |
| No | 15 (75.0) |
| Yes | 5 (25.0) |
| 1 | 2 (40.0) |
| >1 | 3 (60.0) |

<40 kg body weight if ≥12 years.
Patient with mild disease at baseline had severe disease at study entry..

# HAVEN 2
## Bleed-related endpoints

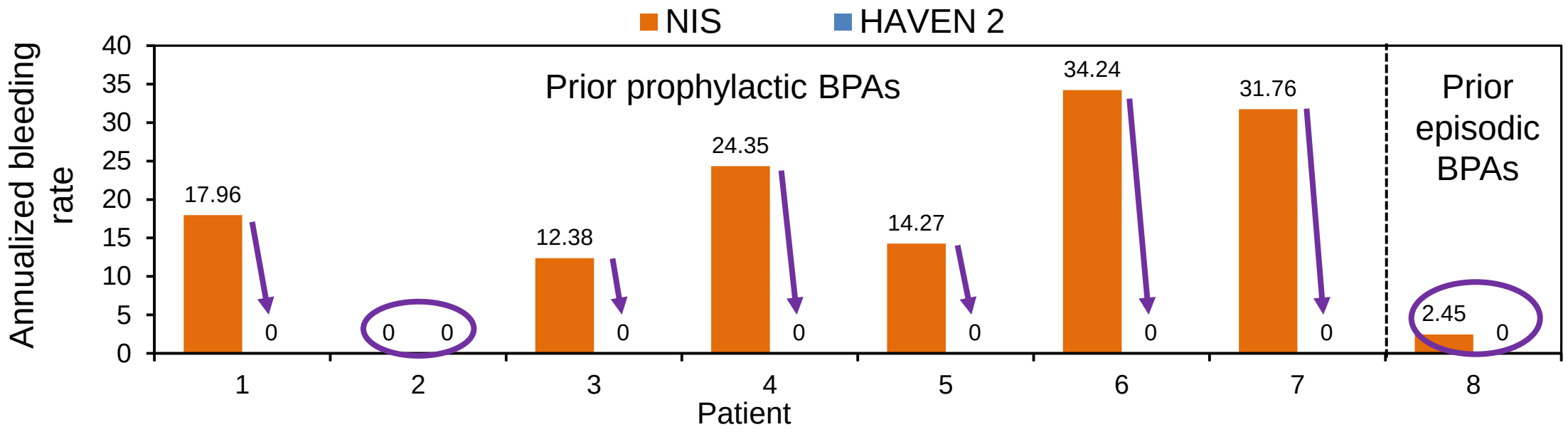
| Endpoint | Mean ABR (95% CI) N=10 | % zero bleeds (95% CI) N=19 |
|---|---|---|
| Treated bleeds | **0.4** (0.00; 4.51) | **94.7** (74.0; 99.9) |
| All bleeds | **3.7** (0.94; 9.81) | **63.2** (38.4; 83.7) |
| Treated spontaneous bleeds | **0.4** (0.00; 4.51) | **94.7** (74.0; 99.9) |
| Treated joint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

Efficacy analyses include only patients <12 years of age.
ABR, annualized bleeding rate; NA, not available.

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




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

- Intra-individual comparison performed for 8 NIS patients on HAVEN 2 study ≥12 weeks
- Zero bleeds reported for all 8 patients receiving emicizumab (efficacy period 85–99 days)

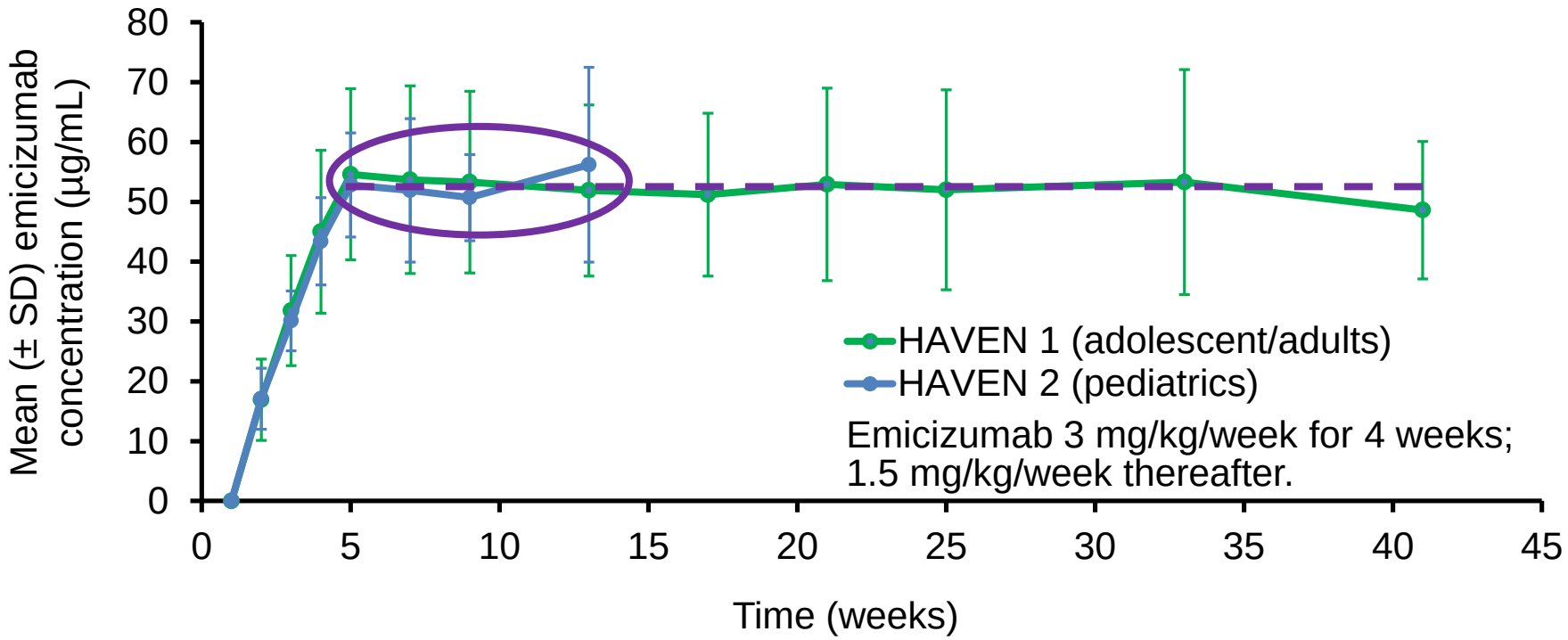
- Substantial reductions in treated bleed rates with emicizumab prophylaxis vs prior BPA treatment

# HAVEN 2 safety summary

| Adverse events, n (%) | Emicizumab 1.5 mg/kg QW (N=20) |
|---|---|
| **Total number of AEs** | 43 |
| **Total patients experiencing ≥1 AE, n (%)** | 14 (70.0) |
| Serious AE | 3 (15.0) |
| Grade ≥3 AE | 3 (15.0) |
| **Related AE** | **3 (15.0)** |
| 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

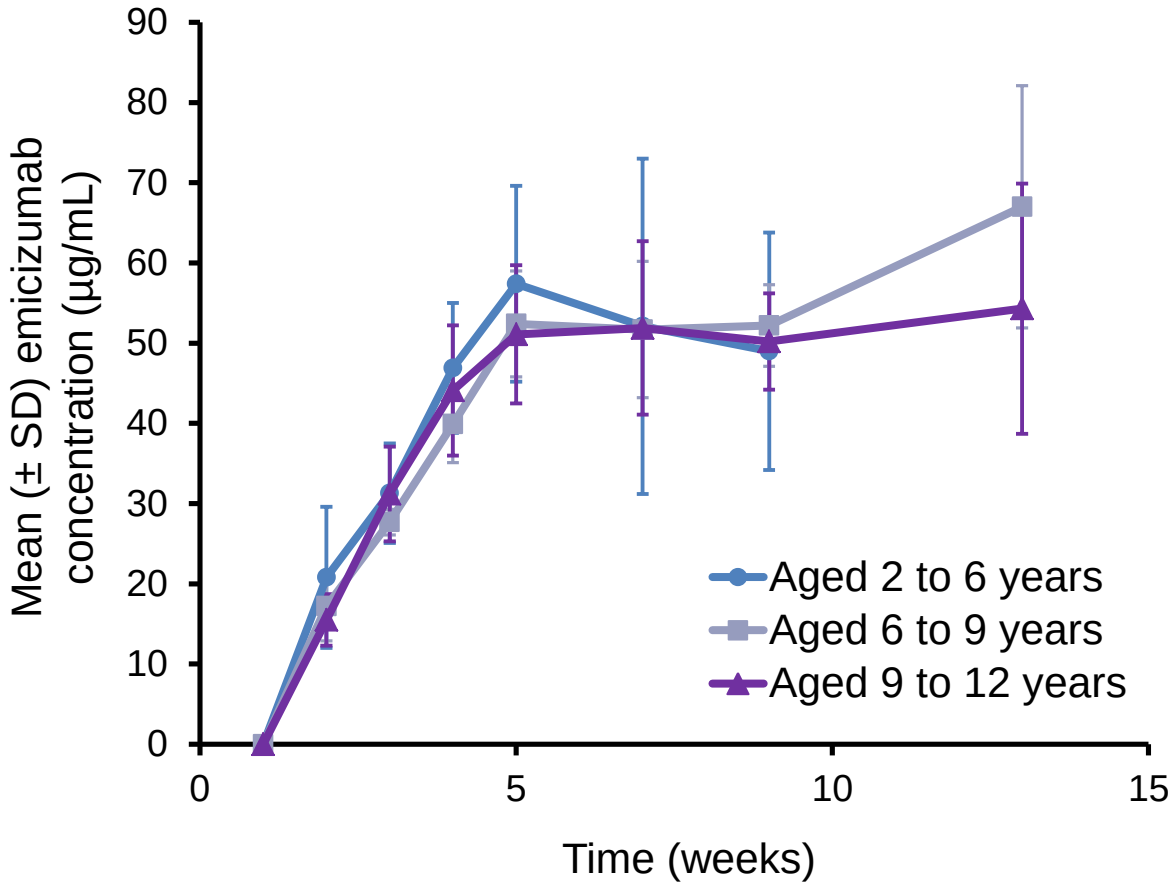


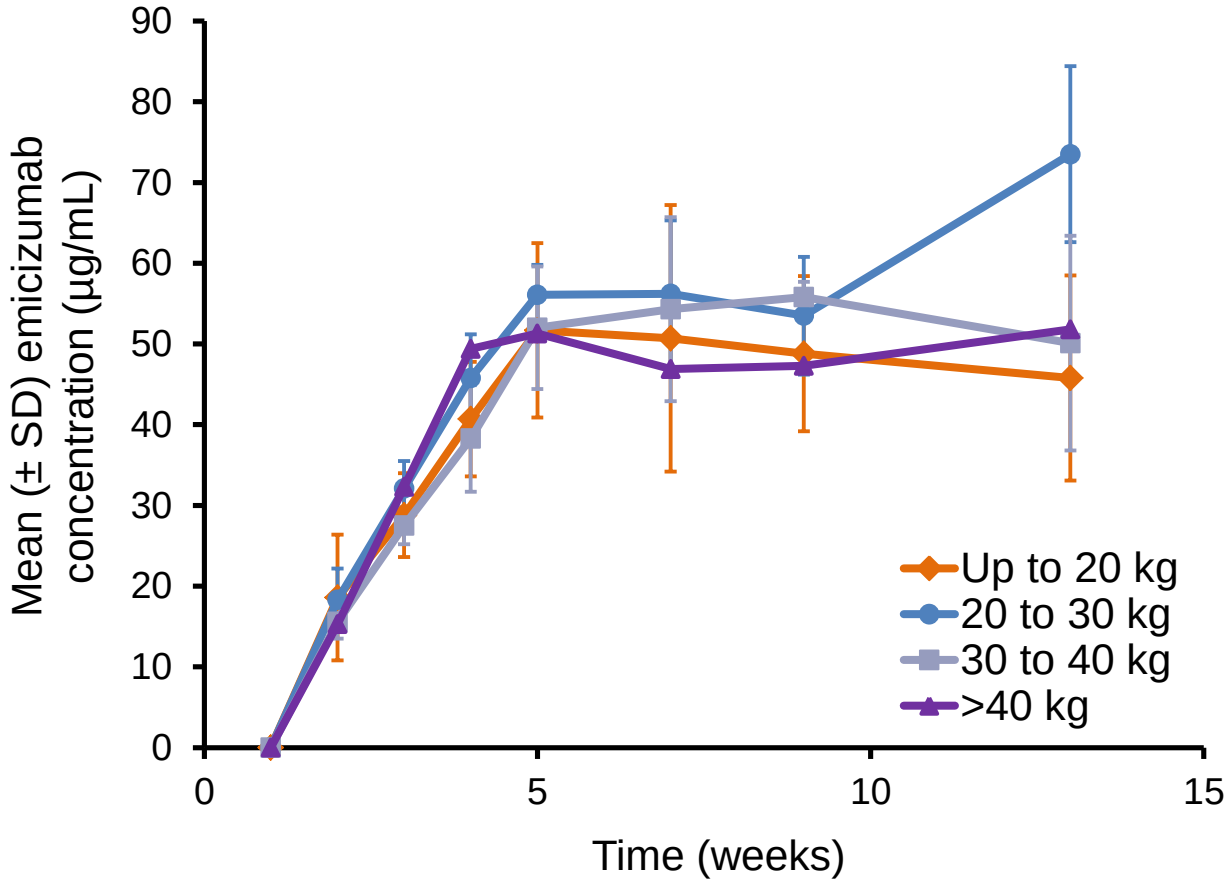

- Target emicizumab exposure was ≥45 µg/mL
- Emicizumab PK profile comparable with that seen in adolescent/adult PwHA
- With weekly subcutaneous dosing, mean trough emicizumab plasma concentrations >50 µg/mL were achieved and sustained once at steady-state

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

Four loading doses of emicizumab 3 mg/kg/wk followed by maintenance doses of 1.5 mg/kg/wk.
SD, standard deviation.

# 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 ≥52 weeks
- Data from this study have been submitted for approval consideration to the EMA and the US FDA

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