# R&D Conference Call (ISTH 2017)

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July 11, 2017

# Emicizumab (ACE910) Development Programs

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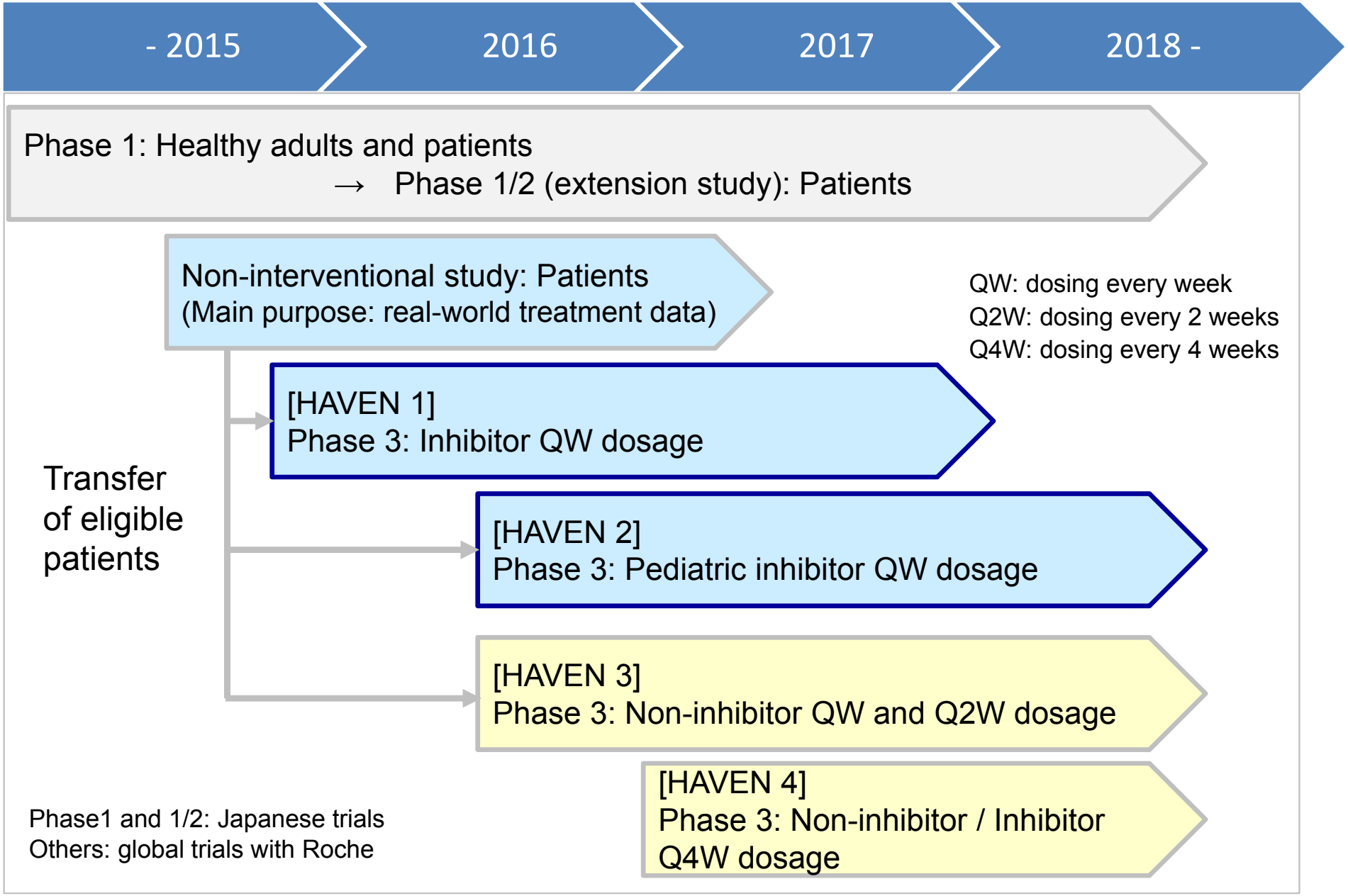

# HAVEN 1 Study / HAVEN 2 Study Interim Analysis

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July 11, 2017

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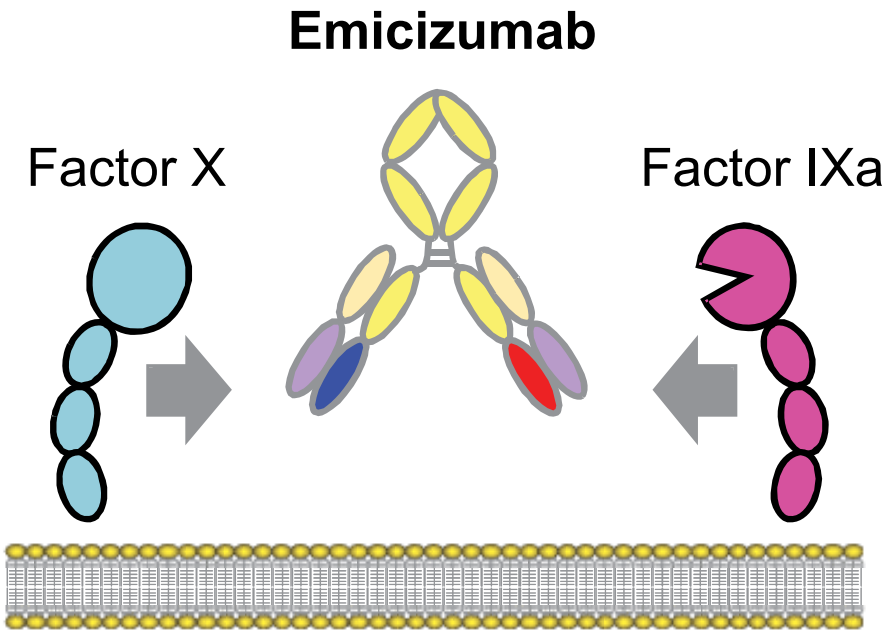
*Emicizumab is an investigational product and is not approved or licensed for the treatment of patients with hemophilia A or any other medical condition*

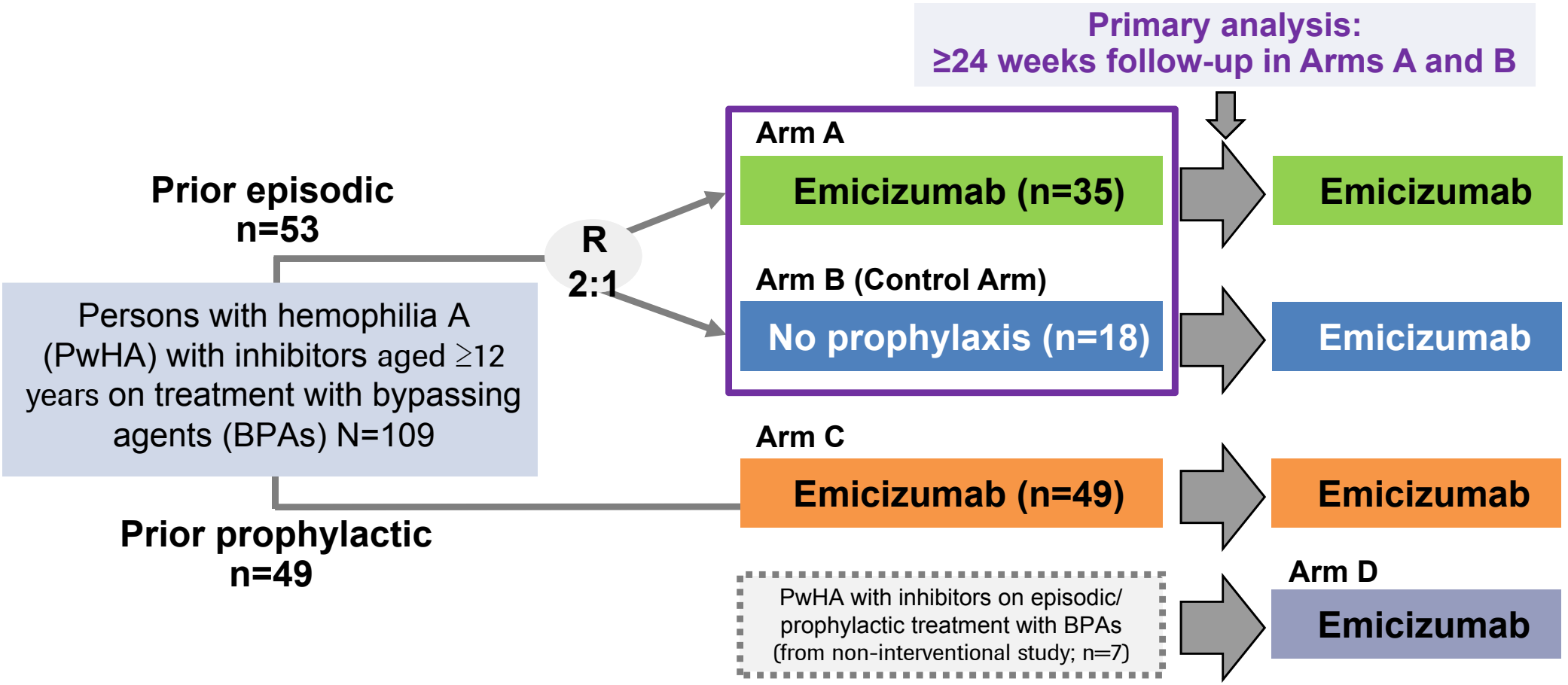
# Emicizumab (ACE910)
## Humanized bispecific monoclonal antibody




- 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

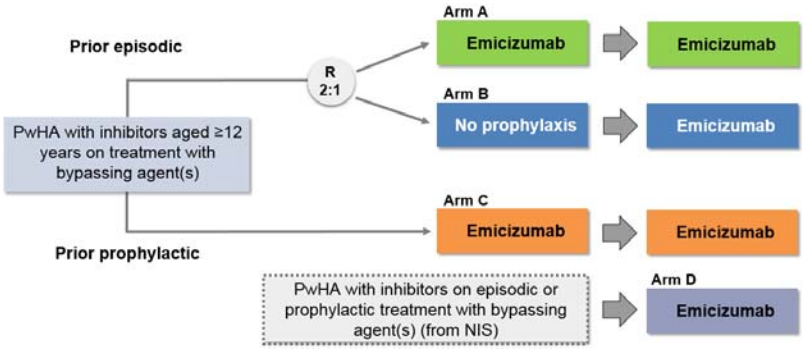
Kitazawa T, et al. *Nat Med* 2012;18:1570–4.
Sampei Z, et al. PLoS One 2013;8:e57479.
Uchida N, et al. *Blood* 2016;127:1633–41.
Shima S, et al. *N Engl J Med* 2016;374:2044–53.

# 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.

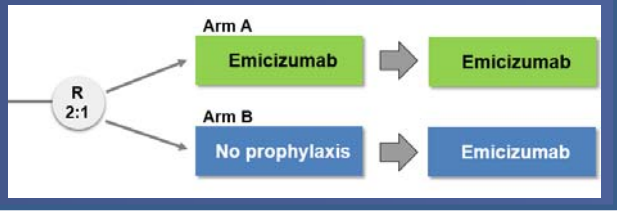
# HAVEN 1
## Demographics/baseline disease characteristics

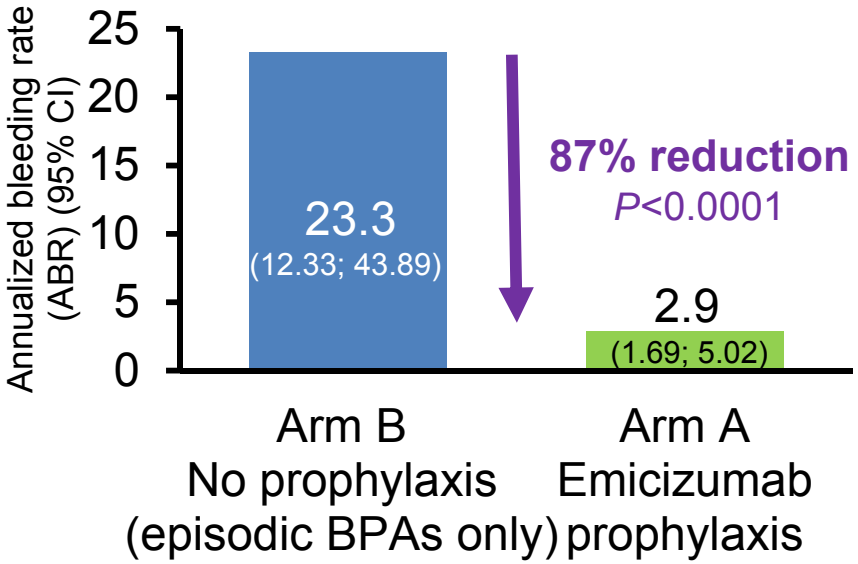



| | Arm A: Emicizumab prophylaxis *(prior episodic BPAs)* n=35 | Arm B: No prophylaxis *(prior episodic BPAs; control arm)* n=18 | Arm C: Emicizumab prophylaxis *(prior BPA prophylaxis)* n=49 | Arm D: Emicizumab prophylaxis *(prior BPAs; episodic or prophylactic)* n=7 | Total N=109 |
|---|---|---|---|---|---|
| **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) |

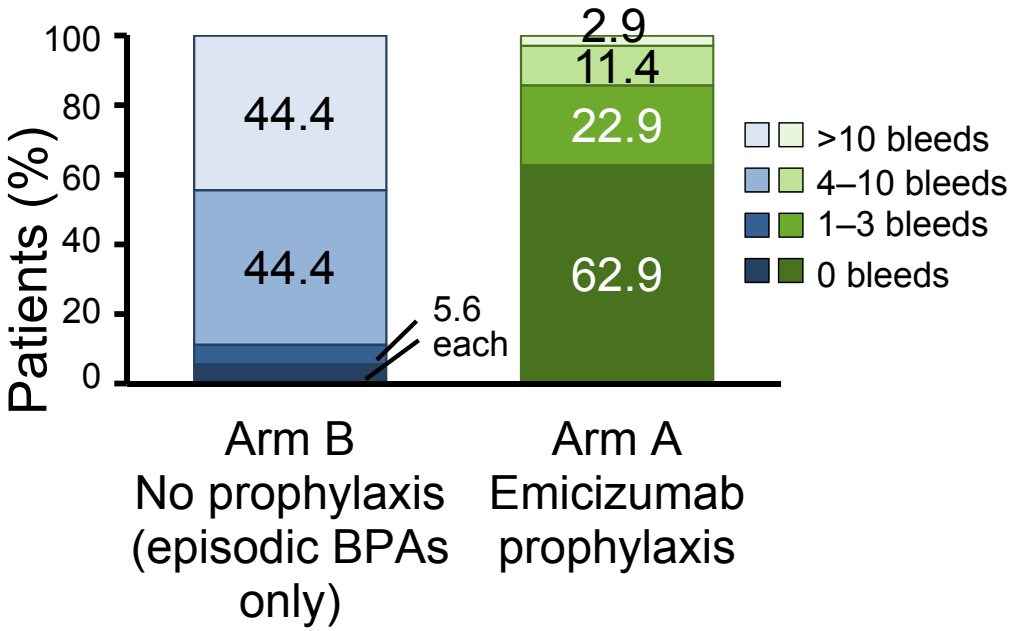
BU, Bethesda units; ITI, immune tolerance induction.

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




| | Arm B | Arm A |
|---|---|---|
| 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.

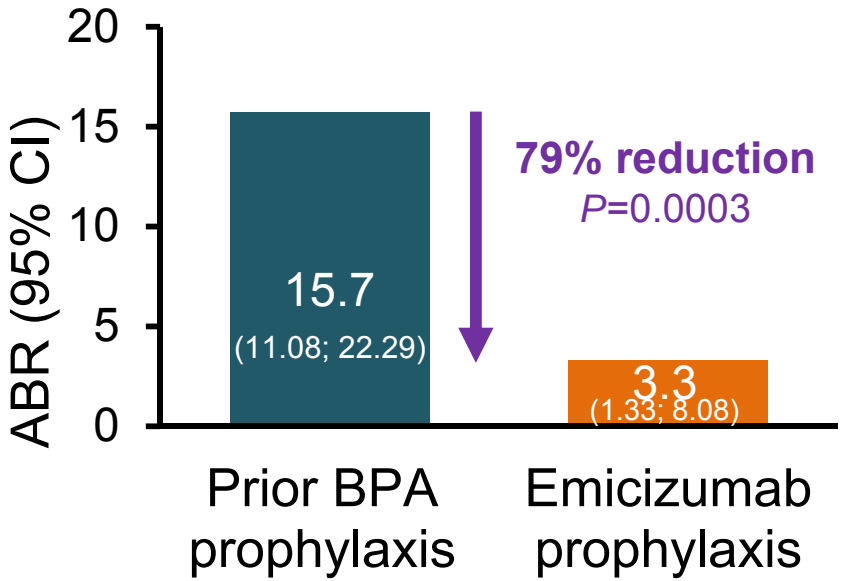
Primary analysis data cutoff – October 25, 2016

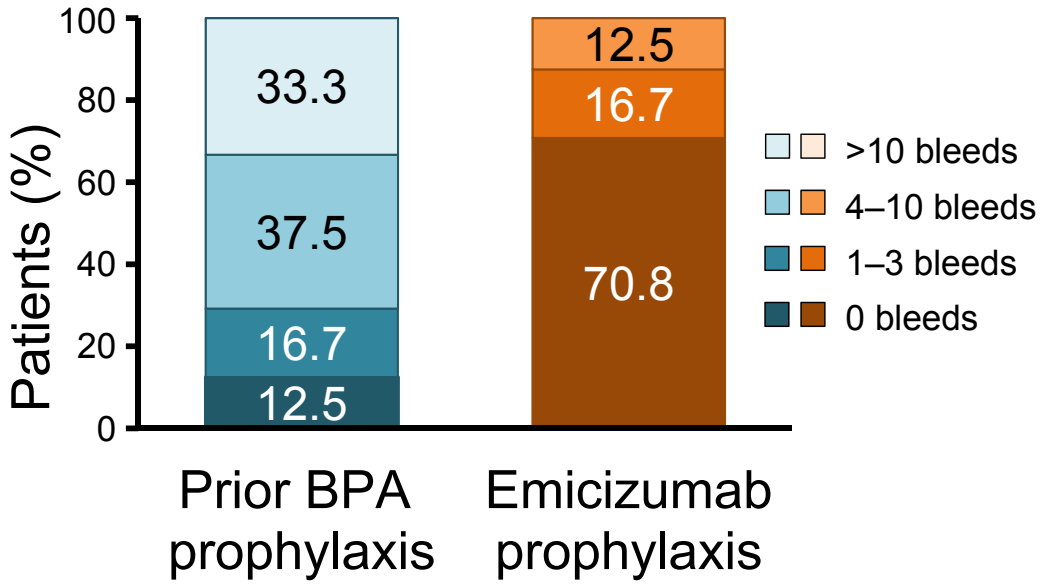
# HAVEN 1 secondary bleed-related endpoints
## Consistent statistically significant reductions in ABR

| | 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.

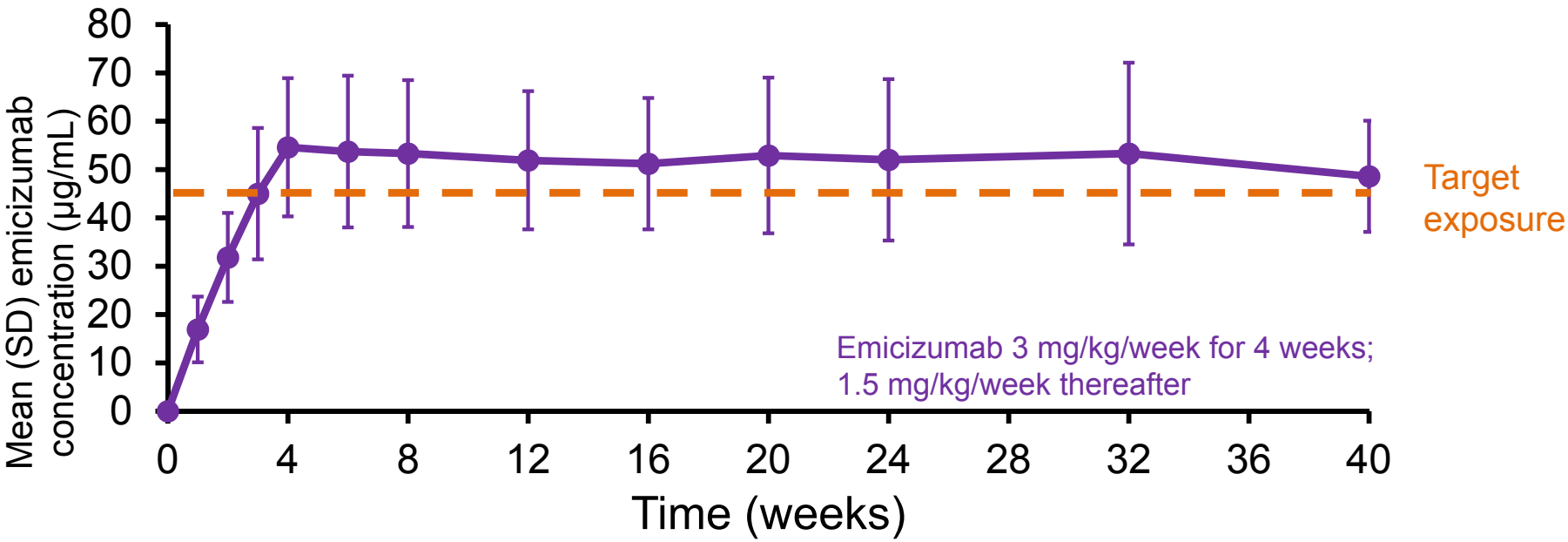
# HAVEN 1 health-related quality of life and health status
## Randomized comparison

| 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.

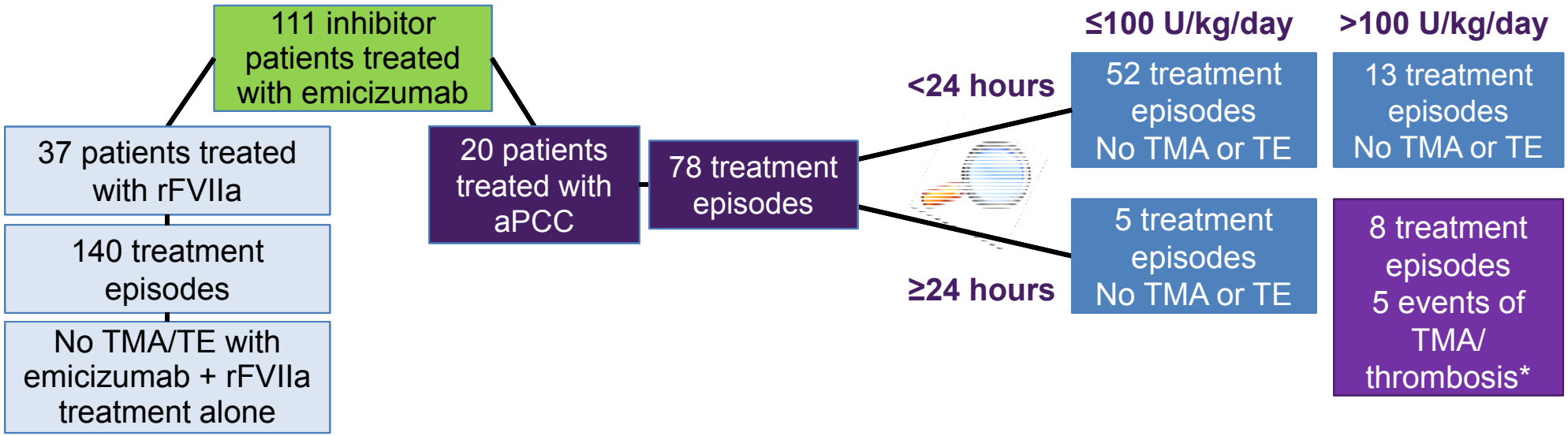
# HAVEN 1
# Characteristics of TMA and thrombotic events

| 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)

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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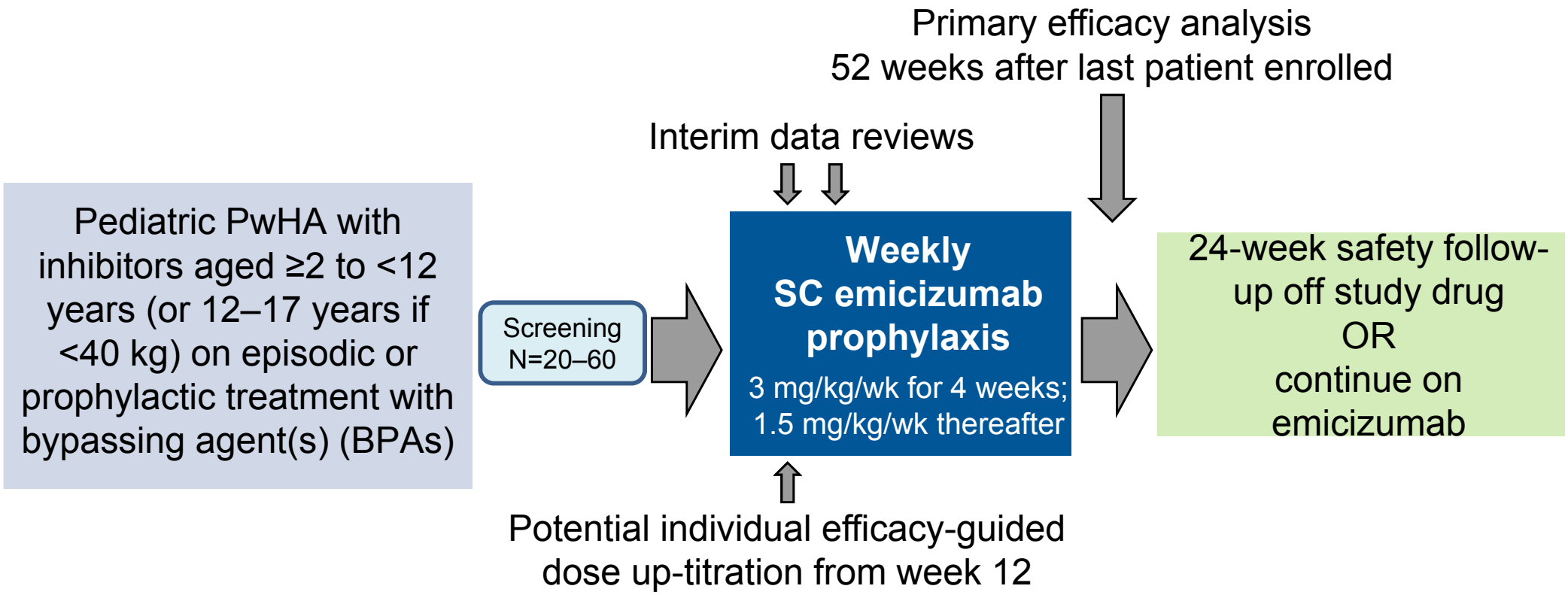
[1]Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA, USA; [2]Universitätsklinikum Bonn, Bonn Germany; [3]North London Paediatric Haemophilia Network, London, UK; [4]University Hospital La Paz, Madrid, Spain; [5]Angelo Bianchi Bonomi Hemophilia 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

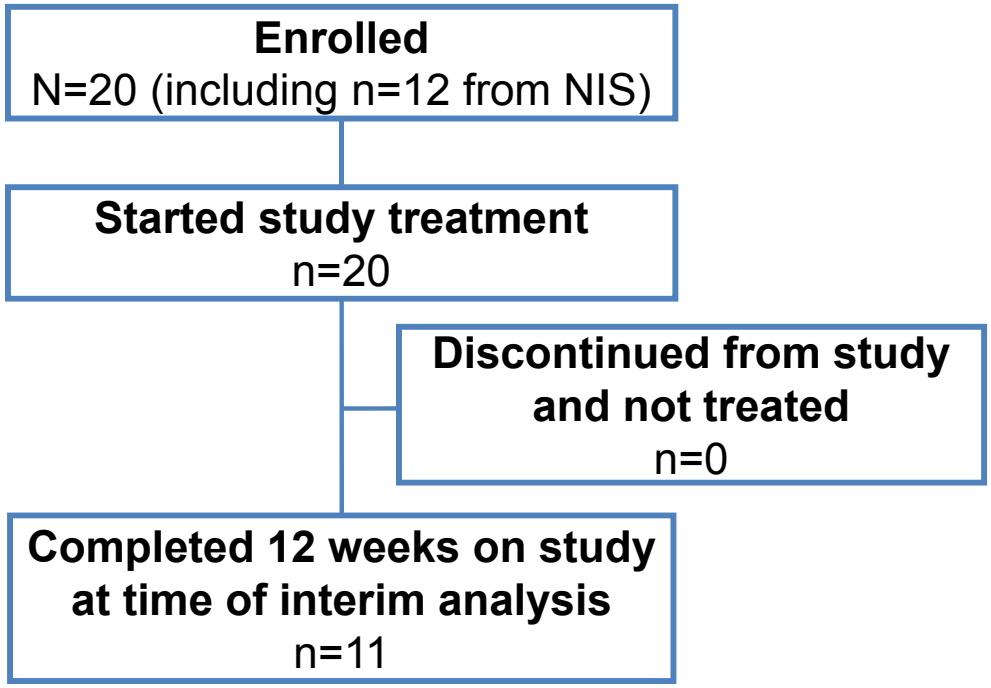
*Emicizumab is an investigational product and is not approved or licensed for the treatment of patients with hemophilia A or any other medical condition*

# 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 ≥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

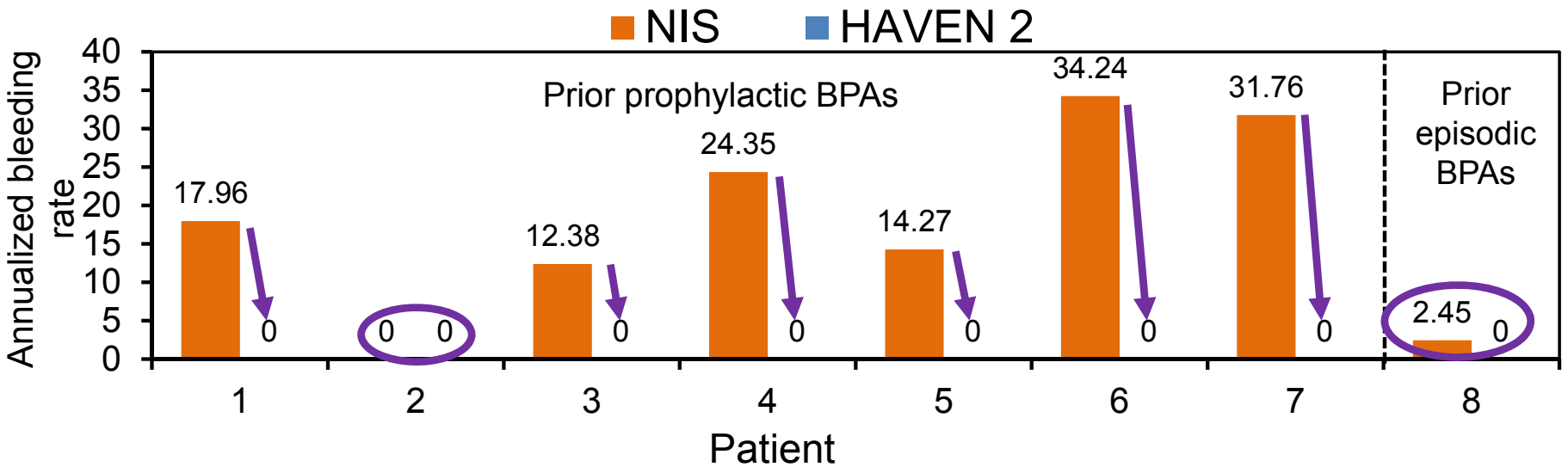
| Endpoint | Mean ABR (95% CI) N=10 | % zero bleeds (95% CI) N=19 |
|---|---|---|
| Treated bleeds | **0.4** (0.00; 4.51) | **94.7** (74.0; 99.9) |
| All bleeds | **3.7** (0.94; 9.81) | **63.2** (38.4; 83.7) |
| Treated spontaneous bleeds | **0.4** (0.00; 4.51) | **94.7** (74.0; 99.9) |
| Treated joint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

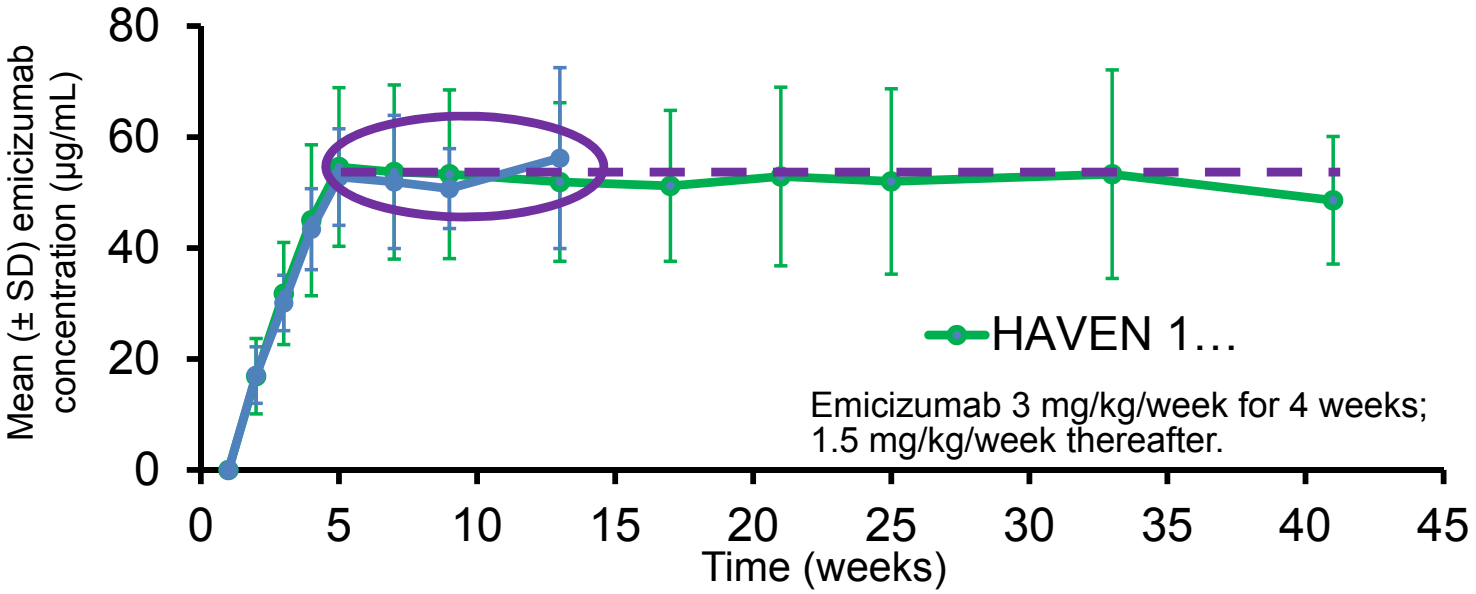
- Substantial reductions in treated bleed rates with emicizumab prophylaxis vs prior BPA treatment

# 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

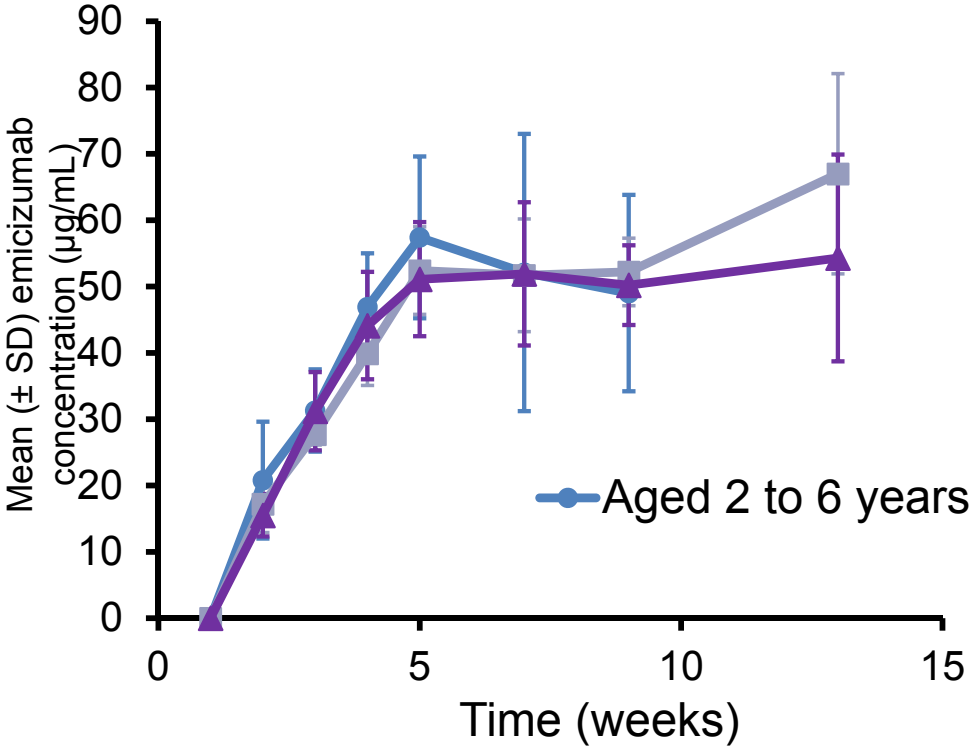
# HAVEN 2
## Emicizumab pharmacokinetics

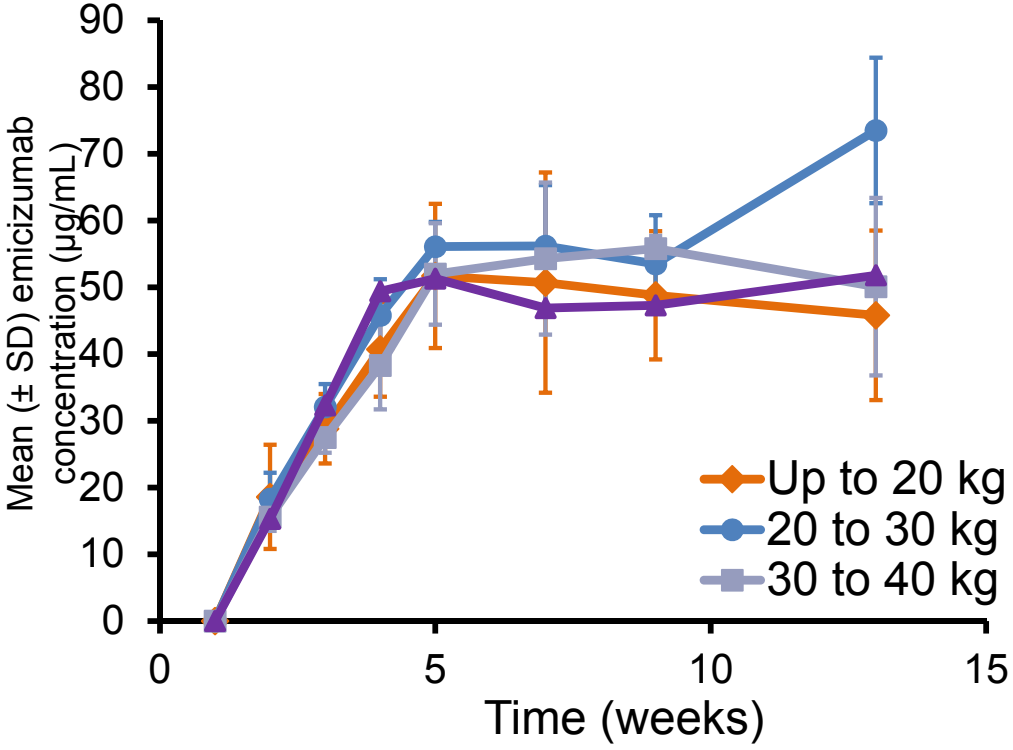



- Target emicizumab exposure was ≥45 µg/mL
- Emicizumab PK profile comparable with that seen in adolescent/adult PwHA
- With weekly subcutaneous dosing, mean trough emicizumab plasma concentrations >50 µg/mL were achieved and sustained once at steady-state

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

Innovation all for the patients

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# Forward-Looking Statements

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the "Company"). These statements reflect the Company's current analysis of existing information and trends. Actual results may differ from expectations based on risks and uncertainties that may affect the Company's businesses.

Although this presentation includes information regarding pharmaceuticals (including products under development), the information is not intended as any advertisement and/or medical advice.

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