Using a non-interventional study to strengthen the evidence collected in a Phase III program: a Hemophilia A case Study

June 27, 2018

EFSPI Small populations and level of evidence

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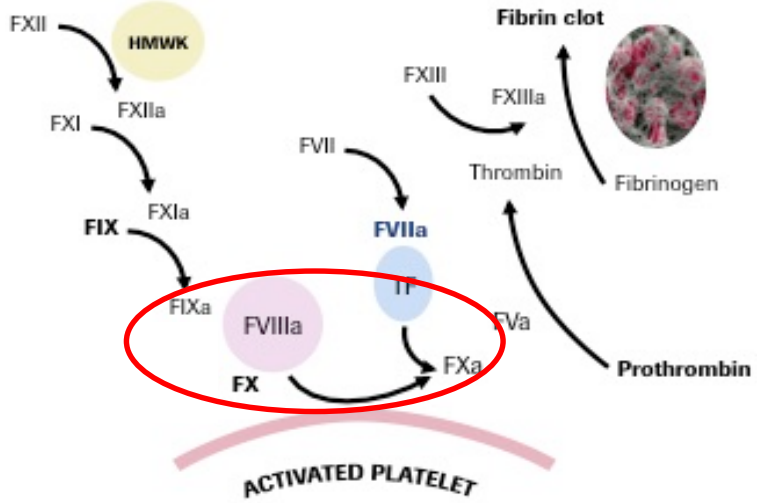
Outline

- Disease background
- Problem statement
- Set up of the NIS
- Key benefits of the NIS
- Results
- Conclusions

Disease Overview

Disease Background

- Haemophilia A commonly caused by deficiency of FVIII
- Severity (FVIII activity): mild (6-40%), moderate (1-5%), severe (<1%). 60-70% are severe.
- 1:5000 male births
- The hallmark of haemophilia is bleeding
  - easy bruising
  - spontaneous/prolonged bleeding into joints & muscles
- Recurrent joint bleeds → significant morbidity and disability

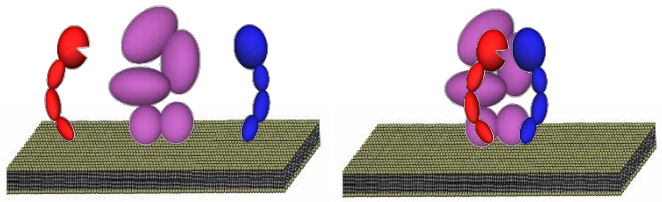


Treatment Paradigms

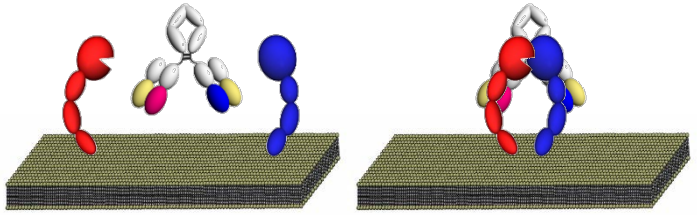
- Treatment with replacement FVIII therapy (IV), but 25-30% of patients develop FVIII inhibitors
- Episodic treatment: goal is to treat bleeds
  - FVIII for non-inhibitor patients
  - Bypassing agents (rFVII or aPCC) for inhibitor patients
- Prophylactic treatment: goal is to prevent bleeds
  - FVIII for non-inhibitor patients: achieves median ABR 0-2 with 2-3X/week IV infusion
  - aPCC for inhibitor patients: median ABR 8 with every other day IV infusion

Emicizumab: FIXa/FX Bispecific MAb

Mechanism of action of FVIII



Mechanism of action of emicizumab



Potential advantages of emicizumab

- Subcutaneous administration
- Less frequent injections (every week, every 2 weeks or every 4 weeks) due to long half-life
- Not expected to induce FVIII inhibitors
- Decreased treatment burden and more effective prophylaxis

First significant advancement in 30 years

Kitazawa et al., Nat Med (2012), 18:1570-4

Problem statement

- Limited literature and standards available for data collection and endpoint definitions
  - ABR=annualized bleeding rate «standard endpoint» but no consistency in how data was collected, endpoint defined and estimated → no standard estimand
  - Majority of bleeds diagnosed and treated at home → data collected directly from patients
- No in-house experience in hemophilia A
- First study pivotal phase III; FVIII replacement prophylaxis a high bar
- Desire to move fast given high unmet need and outstanding Phase 1 data
- Limited literature available, especially in the inhibitor population, to have a good understanding of expected control arm efficacy
- Natural bleeding tendency between patients varies a lot which impacts interpretation of between patient comparisons in fairly small studies and patients perceive the bleeds

Solution

- Let’s run a study to:
  - Try out how the data collection through an ePRO works and how compliant the patients are
  - Test in house developed “bleed and medication questionnaire” and validate it → possibility to optimize for phase III
  - Learn from the data to better define the endpoints
  - Get a better understanding of the bleed rates to inform sample size estimation
  - Serve as a lead-in to Phase III studies to provide us within-patient efficacy data

- And let’s do this in a flexible way which does not delay the start of phase III

Particularities of Hemophilia A

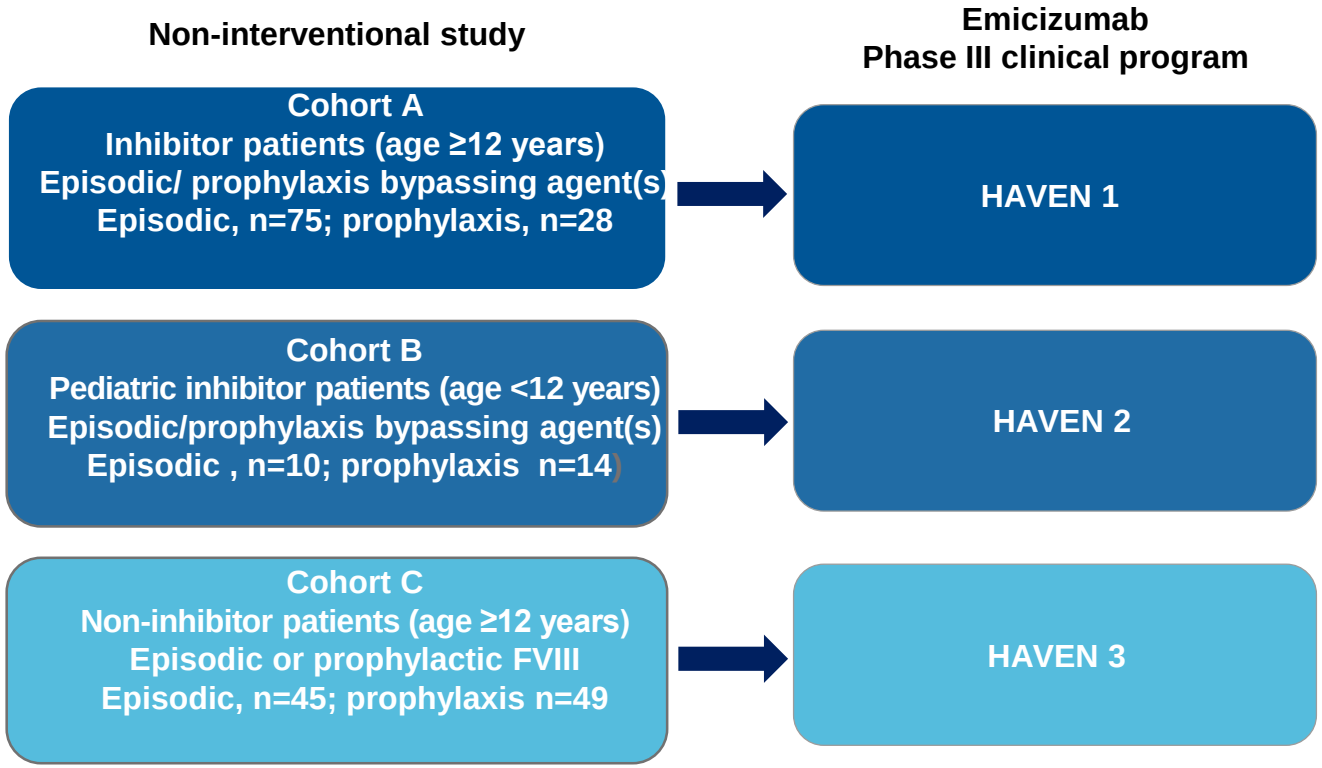
- Hemophilia A is a non-progressive disease
- Current FVIII and BPA therapies have very short half lives → no carry over effect
  - Emicizumab has a long half life → cross-over study not possible
- A blinded study has never been done in hemophilia A and would not be feasible due to route of administration in patient population with bleeding phenotype
- Patients diagnose bleeds and make the decision to treat mainly at home → reporting bias
- Heterogeneous disease, highly variable natural bleeding tendency due to e.g. level of FVIII deficiency, physical activity
- Prognostic/predictive factors are not well known or do not exist → not possible to e.g. stratify randomization or adjust for external control

What did we learn?

- We got to build relationships with the investigators and sites and identify patients for the phase III program
  - Enrollment to all studies was *very* fast
- The bleed and medication questionnaire was well designed and patients remained compliant
- ...but ePRO vendor oversight was a lot of work
- It was extremely important to have detailed data early on to facilitate prospective definitions of endpoints for phase III studies
- Running the NIS under a separate protocol gave us flexibility

In conclusion, NIS helped us to have more robust phase III program

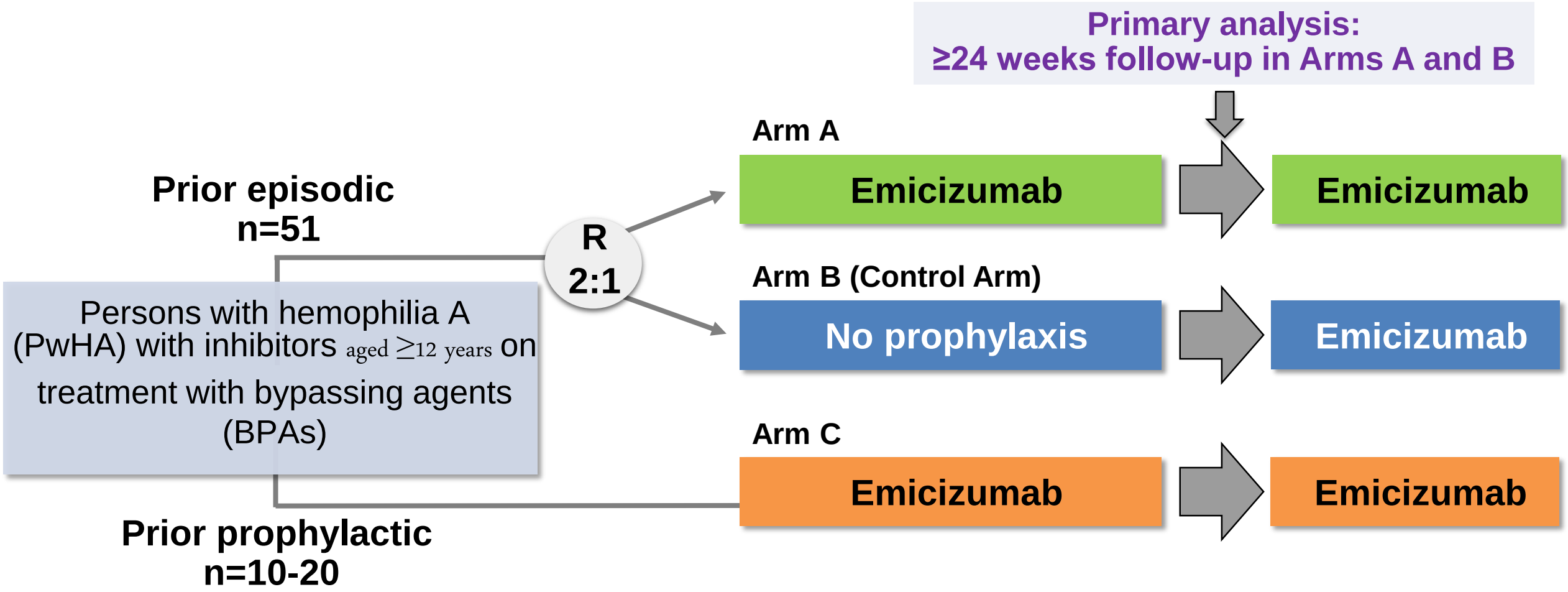
Intra-patient comparison



Patients rolled over from the NIS to phase III studies

This allowed for an intra-patient comparison

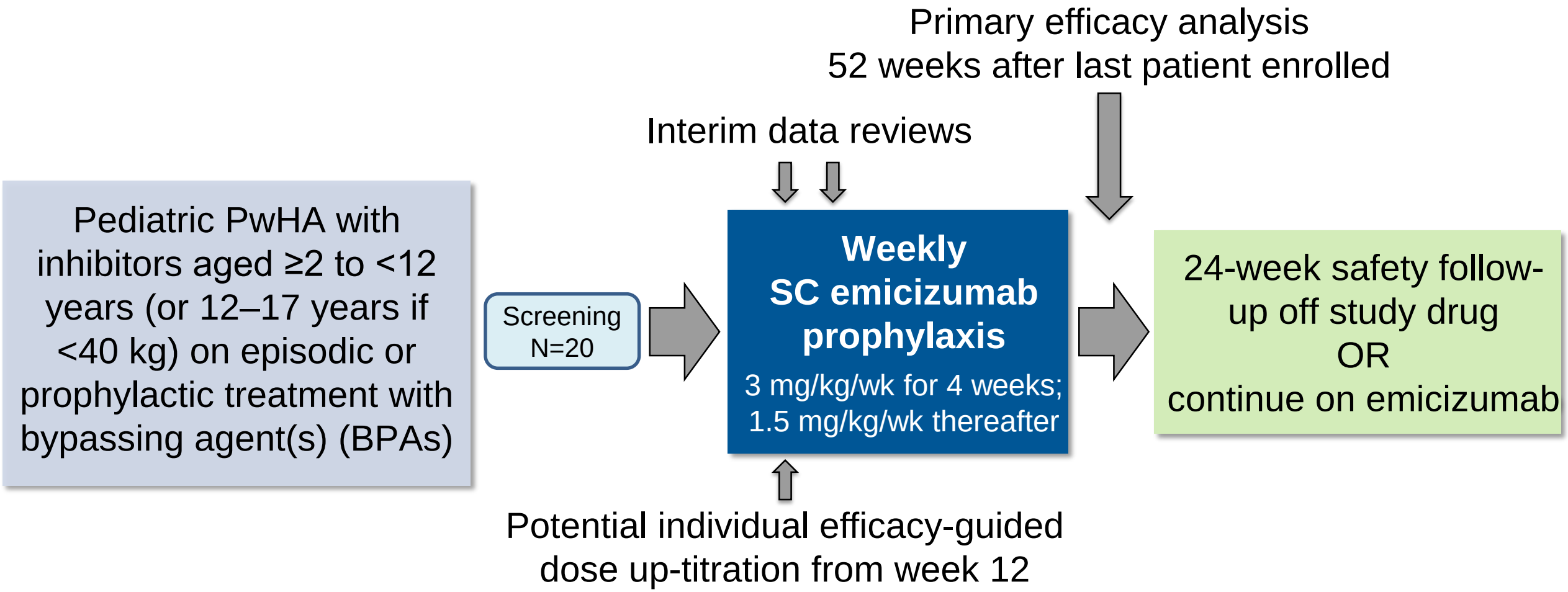
HAVEN 1 original study design



HAVEN 3 study with a very similar design

NCT02622321: phase 3, open-label, multicenter, randomized study
Emicizumab 3 mg/kg/week for 4 weeks; 1.5 mg/kg/week thereafter

HAVEN 2 original study design



NCT02795767.
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.

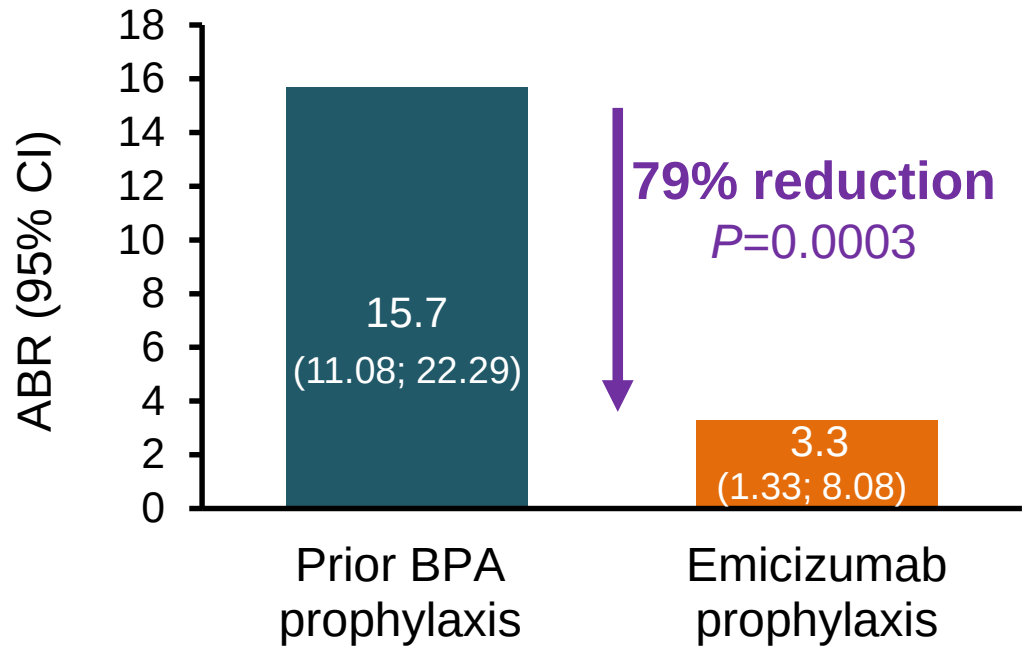
Clinical development plan

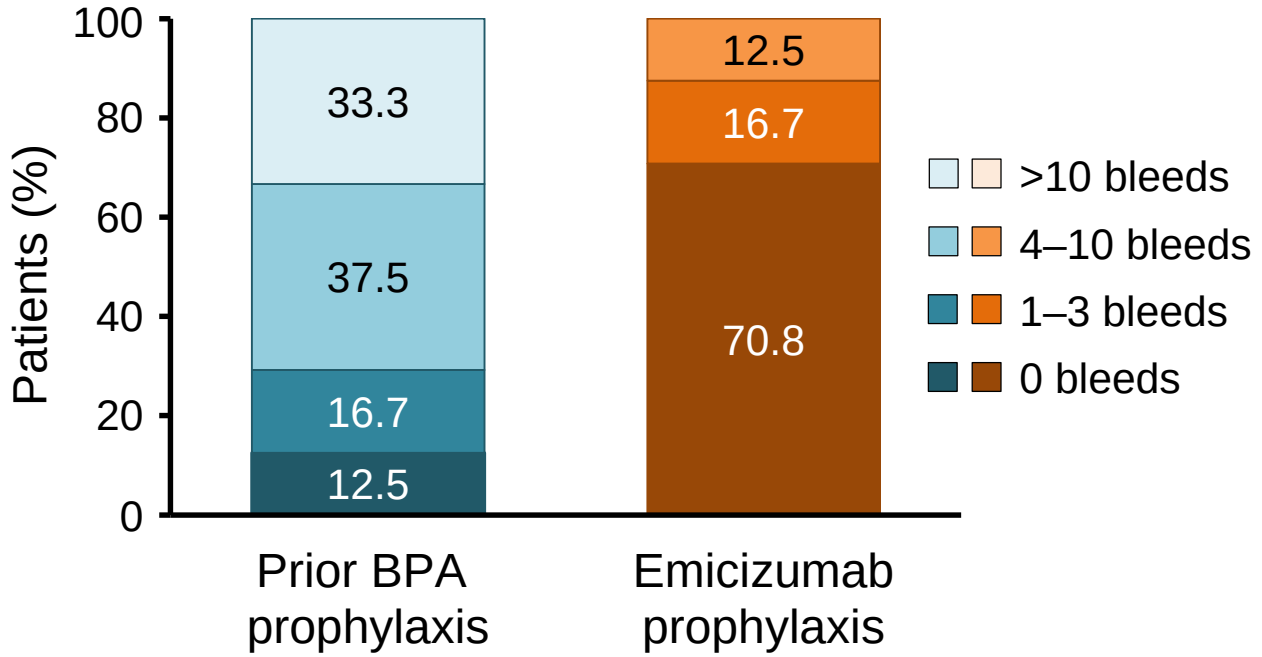
- Feedback from experts was that due to rarity of disease studies will be hard to enroll
- HAVEN 2 set up as a one arm study with PK extrapolation strategy for efficacy with HAVEN 1
- HAVEN 1 and HAVEN 3 primary endpoint comparison against episodic treatment
  - Though prophylaxis generally accepted optimal treatment, large proportion of patients globally still on episodic treatment
  - Adequately powered comparison against prophylactic treatment would have required too many patients and/or a non-inferiority study in non-inhibitor patients

→ NIS provided a comparator arm for HAVEN 2 and a confirmatory, type 1 error controlled comparison against prophylactic treatment for HAVEN 1 and HAVEN 3

Note, all studies were amended to include much larger number of patients than originally planned due to overwhelming interest from patients and sites to participate

HAVEN 1 results



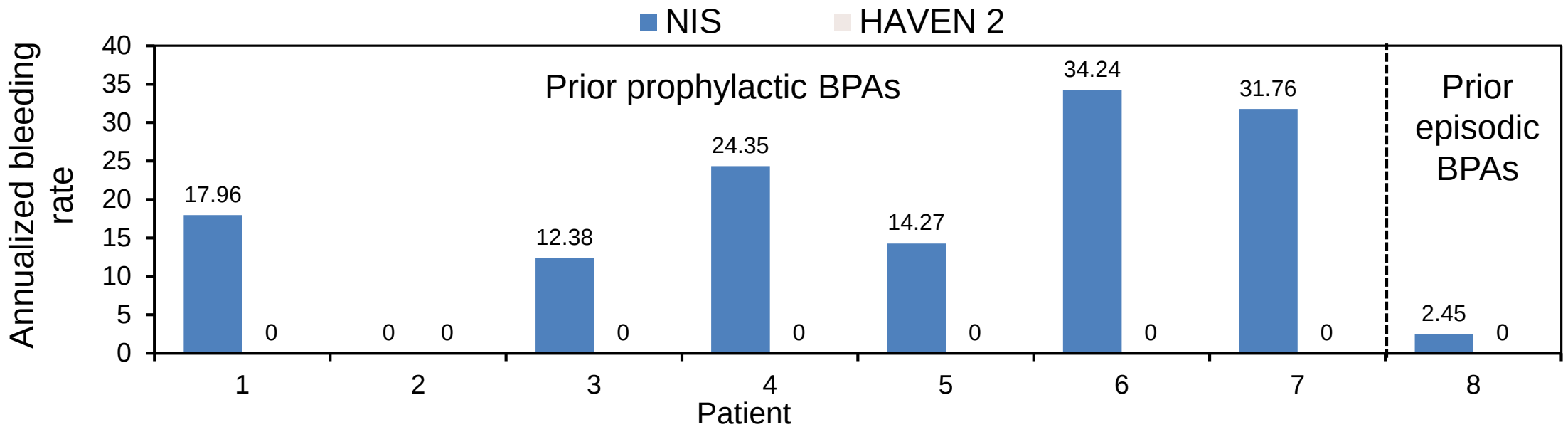


Median ABR (IQR)	**12.0** (5.73; 24.22)	**0.0** (0.00; 2.23)

- 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 2 results



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

Hemlibra USPI

Table 5 Intra-Patient Comparison of Annualized Bleed Rate with HEMLIBRA Prophylaxis versus Previous Bypassing Agent Prophylaxis

Endpoint	HEMLIBRA Prophylaxis (N = 24)	Previous Bypassing Agent Prophylaxis (N = 24)
Treated Bleeds		
ABR (95% CI) [a]	3.3 (1.3, 8.1)	15.7 (11.1, 22.3)
% reduction (95% CI) p-value	79% (51.4%, 91.1%) 0.0003	
% patients with zero bleeds (95% CI)	70.8 (48.9, 87.4)	12.5 (2.7, 32.4)
Median ABR (IQR)	0 (0, 2.2)	12 (5.7, 24.2)

ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile

[a] Based on negative binomial regression.

HAVEN 1

In the intra-patient analysis, 13 pediatric patients who had participated in the NIS had an ABR of 17.2 (95% CI [12.4, 23.8]) on previous bypassing agent treatment (prophylactic treatment in 12 patients and on-demand treatment for one patient). Weekly HEMLIBRA prophylaxis resulted in an ABR for treated bleeds of 0.2 (95% CI [0.1, 0.8]) based on negative binomial regression, corresponding to a 99% reduction in bleed rate. On HEMLIBRA prophylaxis, 11 patients (84.6%) had zero treated bleeds.

HAVEN 2

HA feedback on HAVEN 1 and HAVEN 2

- Initially, clarifications were needed to explain that the NIS is not a “historical control from a registry” or an “external control arm” but a study run like a clinical trial
  - Prospective data collection with same methodology than Phase III
  - It is a true intra-patient comparison, i.e., patients rolled over from NIS to Phase III
- Other main questions were around selection bias at population level and how does the NIS data compare against real world evidence and other clinical trials
  - Due to variety of endpoint definitions used in the past there was a lot of misperception of what the actual expected bleed rates are
  - Compliance to prophylaxis is very important for traditional therapies due to the short half life
- In general, feedback from HAs was encouraging and the intra-patient comparison was considered by some HAs the most important evidence generated
  - Note, HAVEN 3 review currently ongoing
- Feedback received from the scientific community largely similar

CDPs from other companies currently developing molecules in hemophilia A

Next Steps

ATLAS Phase 3 Program Initiated

ATLAS-INH

- Adults and adolescents with hemophilia A or B with inhibitors
- Currently manage bleeds with on-demand bypassing agent therapy
- N~50

2:1 → 9 months fitusiran OR 9 months on-demand BPA

Primary Endpoints:
- ABR†

Secondary Endpoints:
- Spontaneous ABR
- Joint ABR
- QOL (Haem-A-QOL)

ATLAS-A/B

- Adults and adolescents with hemophilia A or B without inhibitors
- Currently manage bleeds with on-demand (OD) factor replacement therapy
- N~100

2:1 → 9 months fitusiran OR 9 months on-demand factor

Primary Endpoints:
- ABR‡

Secondary Endpoints:
- Spontaneous ABR
- Joint ABR
- QOL (Haem-A-QOL)

ATLAS-PPX

- Adults and adolescents with hemophilia A or B with or without inhibitors
- Currently manage bleeds prophylactically
- N~100

6 months PPX factor/BPA → 7 months fitusiran

Primary Endpoints:
- ABR in factor/BPA and fitusiran period

Secondary Endpoints:
- Spontaneous ABR
- Joint ABR
- QOL (Haem-A-QOL)

Patients who complete the study may be eligible for fitusiran treatment in ATLAS-OLE study

†Powered to detect as little as a 60% reduction from control to fitusiran
‡Powered to detect as little as a 50% reduction from control to fitusiran
Fitusiran is an investigational medicine. Its safety and efficacy have not been established by any health authorities.

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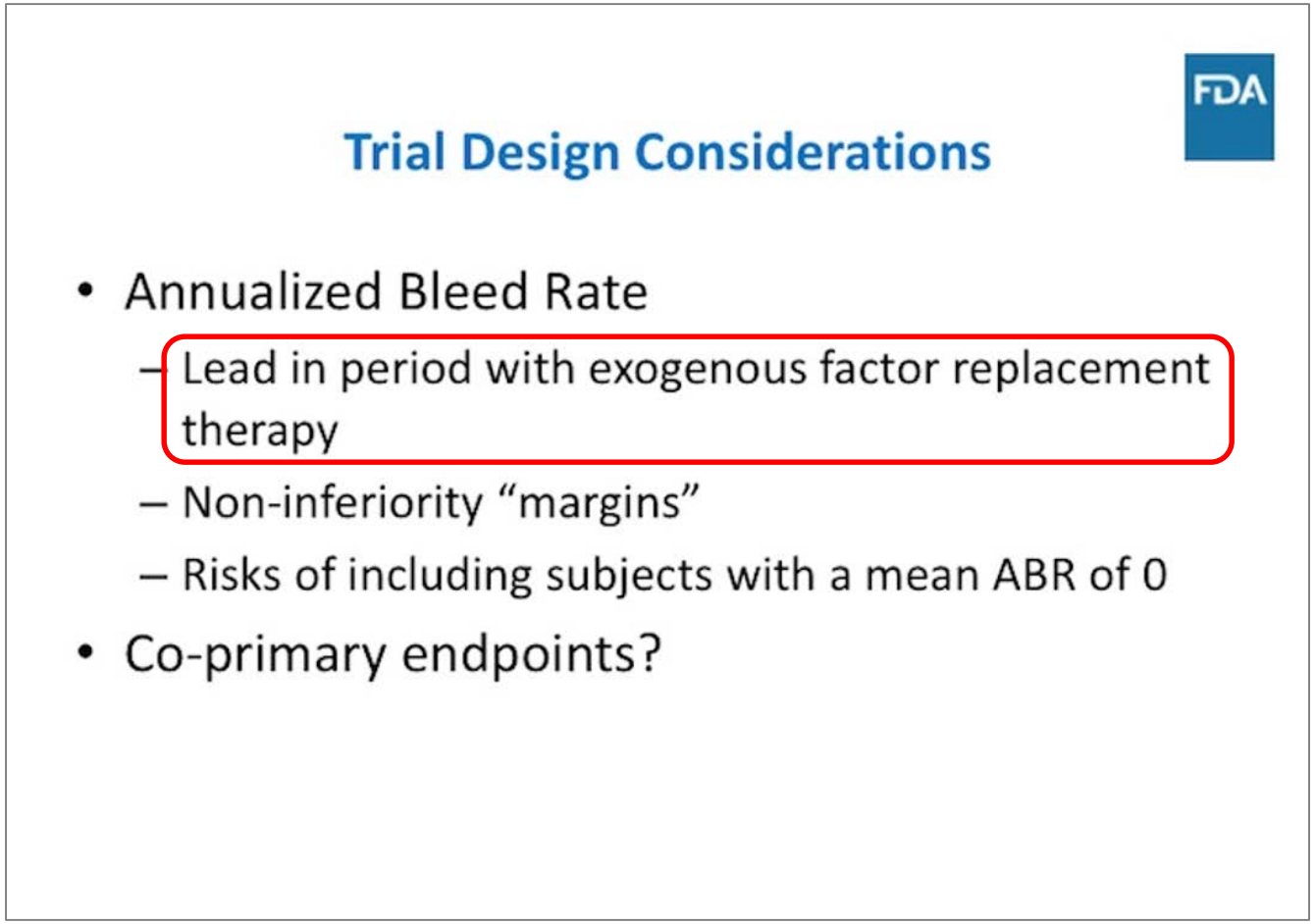
VALOCTOCOGENE ROXAPARVOVEC - CLINICAL STUDIES

- **201** — Phase 1/2 Dose Escalation Study; AAV5-, 4 dose cohorts; UK
- **901** — Global Seroprevalence Study; US, UK, France, Russia, Germany, Italy, Japan, S. Africa, Brazil
- **902** — Non-Interventional Study; US, UK, Spain, Italy, Germany, France, Israel, S. Africa, Brazil, Japan
- **GENEr8-1** — Phase 3 Study with 6E13 vg/kg dose; US, UK, Spain, Italy, Germany, France, Israel, S. Africa, Brazil, Japan
- **GENEr8-2** — Phase 3 Study with 4E13 vg/kg dose; US, UK, Spain, Italy, Germany, France, Israel, S. Africa, Brazil, Japan
- **203** — AAV5+ Phase 1/2 Titer Escalation Study; 2 titer cohorts (≤500, >500); UK

Intra-patient comparison has become a new standard for pivotal trials in hemophilia A

Source: presentations at scientific conference

FDA's position on trial designs in Hemophilia A



Health authorities are proposing an intra-patient comparison

Source: presentation at WFH scientific conference by Ilan Irony from the FDA

Conclusions

- NIS proved to be very useful from learning and operational perspective in a disease area new to the company
- NIS provided the ability to conduct an intra-patient comparison which substantially strengthened the evidence collected in the phase III program
- The results were highly valued by health authorities and scientific community
  - Robust phase III-like prospective data collection key for success
- NIS set a new standard for clinical trials in hemophilia A

Acknowledgements

- Sites, study investigators, patients and their families

- Colleagues at Roche, Genentech and Chugai

Thank you!