Roche Analyst Event at ISTH 2017

Berlin, Monday, 10 July 2017

Agenda

Welcome
Daniel O'Day, CEO Roche Pharmaceuticals

HAVEN1: Ph3 data of emicizumab (ACE910) prophylaxis in adults with hemophilia A with inhibitors
Prof. Dr. med. Johannes Oldenburg, University Clinic Bonn, Institute of Experimental Hematology and Transfusion Medicine

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HAVEN2: Ph3 interim data of emicizumab (ACE910) prophylaxis in pediatrics with hemophilia A with inhibitors; aspects of disease management and emicizumab global development program
Gallia Levy, M.D., Ph.D., Global Development Team Leader emicizumab

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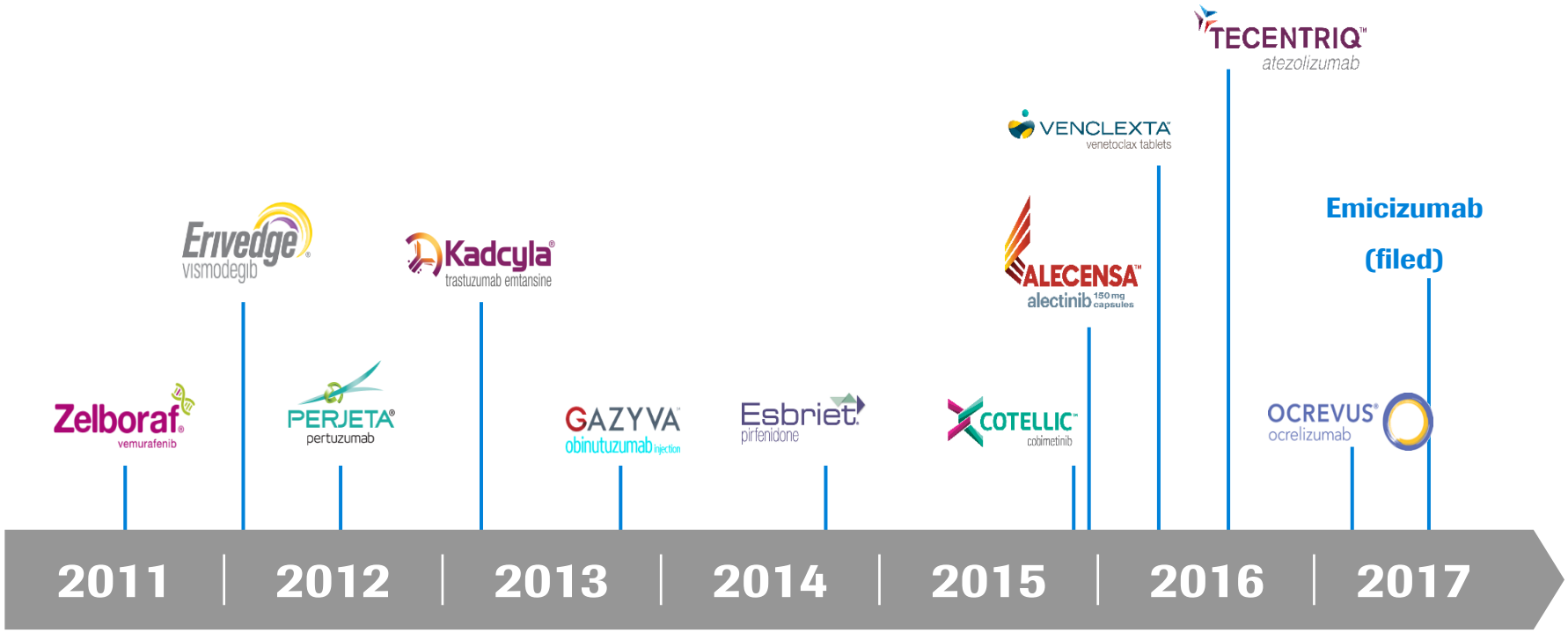
Q&A

Welcome

Daniel O'Day
CEO Roche Pharmaceuticals

Roche is committed to innovation

Heavy launch activities

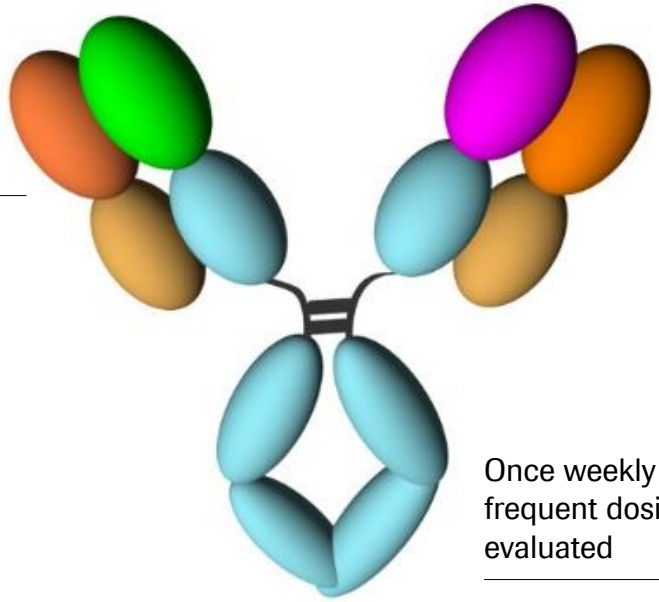


Leading industry with 15 BTDs, 5 recent launches awarded a BTD

BTD=Breakthrough Therapy Designation

Emicizumab: A bispecific monoclonal antibody under investigation for hemophilia A

Bridges factors IXa and X, to activate the natural coagulation cascade and restore the blood clotting process



Expected to avoid the development of factor VIII inhibitors, avoiding a serious complication seen with current factor VIII replacement therapies.

Once weekly subcutaneous injection; less frequent dosing schedules also being evaluated

Emicizumab: Addressing unmet needs in hemophilia A

Treatment benefit

Improved treatment benefit

- Substantially reduced ABR, with zero bleeds in a majority of patients
- Potentially less long-term joint damage and fewer severe /life threatening bleeds
- Prophylactic treatment offers sustained protection

Treatment burden

Reduced treatment burden

- Subcutaneous administration
- Less intensive dosing regime

Quality of life

Improved quality of life

- Reduced bleeds and reduced treatment burden translate into improved quality of life

HAVEN1: Phase 3 study of emicizumab (ACE910) prophylaxis in adults with hemophilia A with inhibitors

Prof. Dr. med. Johannes Oldenburg

University Clinic Bonn, Institute of Experimental Hematology and Transfusion Medicine

HAVEN2: Ph3 interim data of emicizumab (ACE910) in pediatrics with hemophilia A with inhibitors; aspects of disease management and emicizumab global development program

Gallia Levy, M.D., Ph.D.
Global Development Team Leader emicizumab

Aspects of disease management

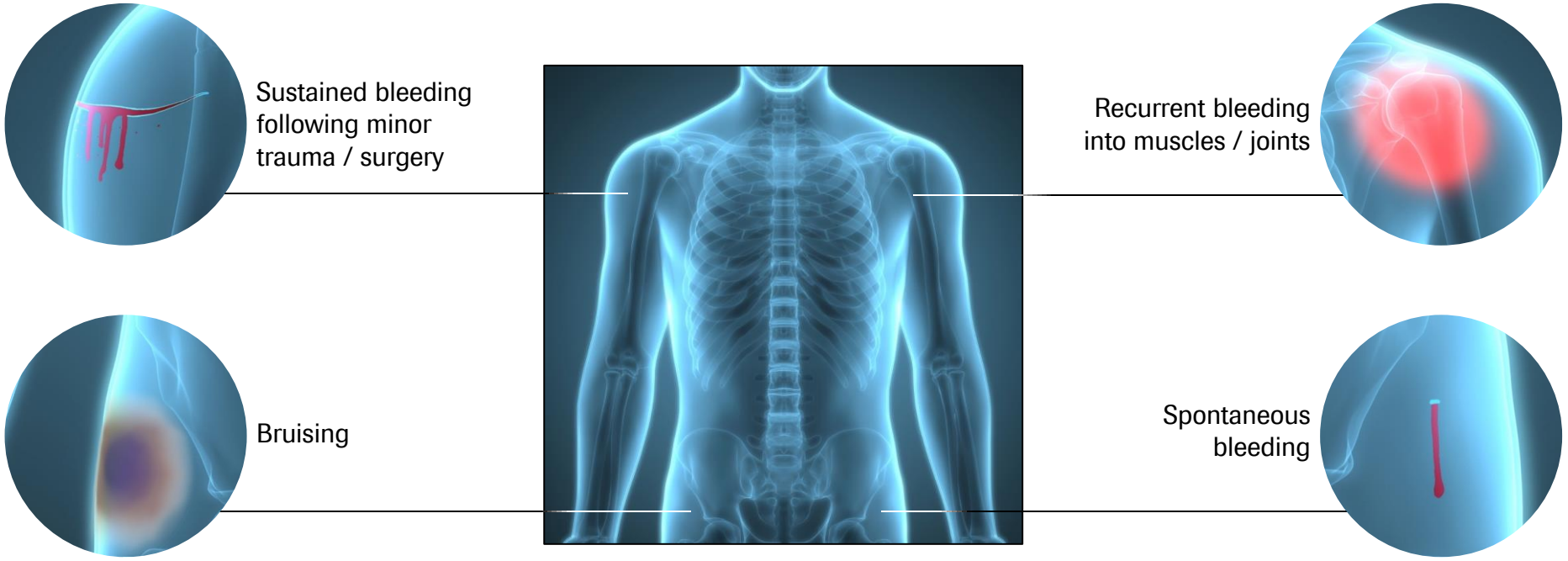
Safety summary HAVEN1

HAVEN2: Ph3 interim data of emicizumab (ACE910) in pediatrics with hemophilia A with inhibitors

Emicizumab global development program

Signs and symptoms of hemophilia

Poor and unpredictable bleed control remains a challenge



World Federation of Hemophilia, Symptoms and diagnosis, 2012

How bleeds have been measured in clinical trials

Self-reporting	Differences in bleeds, disease biology, lifestyle	Bleed definitions

Different calculations

ABR = (number of bleeds x 365.25) / number of days

Negative binomial model

Different measures

Mean ABR

Median ABR

% reduction

% zero bleeds

2014 ISTH Scientific Subcommittee recommendations (Blanchette, Hemostasis Thrombosis 2014)

How bleeds have been measured in HAVEN studies

Self-reporting

Handheld device

Record all bleeds and medications

Differences in bleeds, disease biology, lifestyle

Bleed definitions

- Treated bleeds
- All bleeds
- Spontaneous bleeds
- Treated joint bleeds
- Target joint bleeds

Different calculations

Median: traditional ABR calculation

Estimated ABR and % reductions: Negative binomial model

Different measures

Median ABR

Estimated ABR

% reduction

% zero bleeds

2014 ISTH Scientific Subcommittee recommendations (Blanchette, Hemostasis Thrombosis 2014)

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HAVEN2: Ph3 interim data of emicizumab (ACE910) in pediatrics with hemophilia A with inhibitors

Emicizumab global development program

Safety summary: All emicizumab patients

	HAVEN1 N=103, n (%)
Total number of 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)

No new TMA/thrombotic events occurred when guidance for mitigation was followed

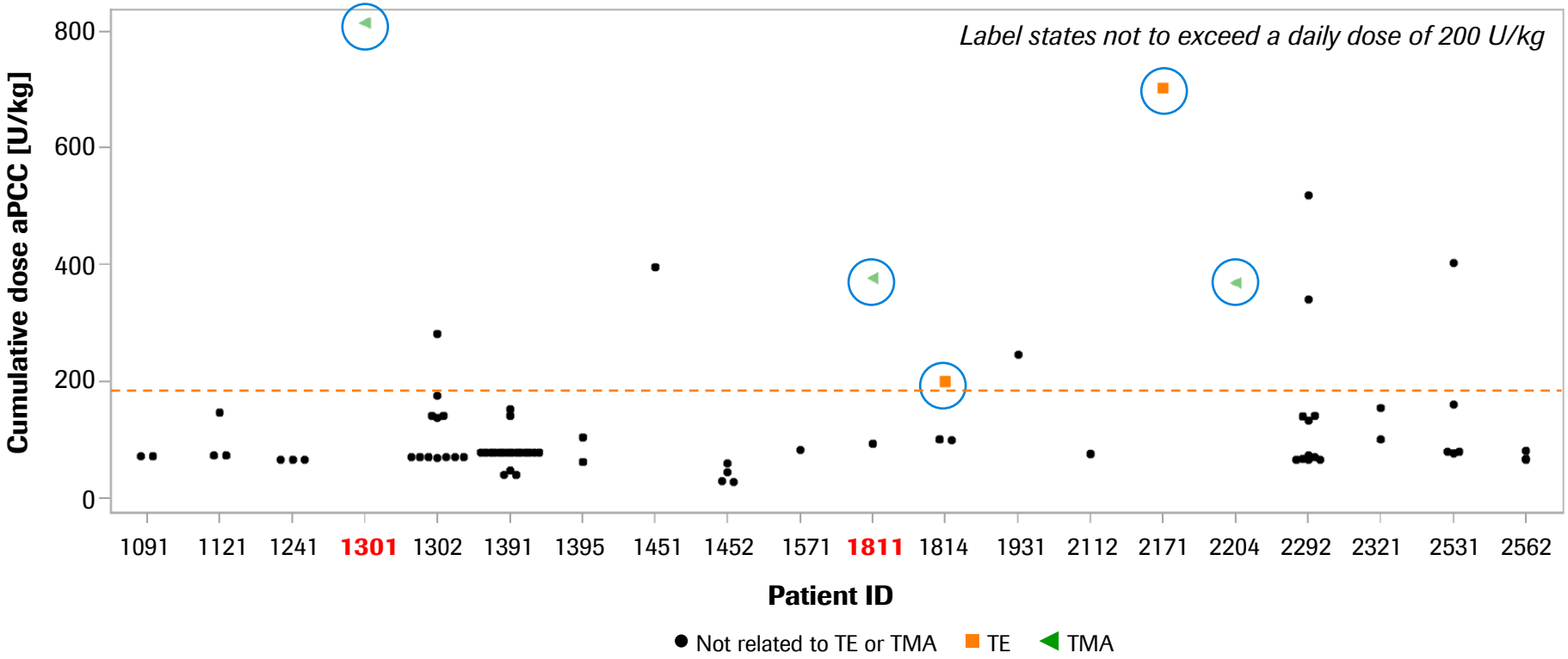
*Additional serious AEs included one event each of: iron deficiency anemia, sepsis, hemarthrosis, muscle hemorrhage, gastric ulcer hemorrhage, headache and hematuria. Two additional withdrawals not related to AEs; one withdrawal by patient, one withdrawal due to physician decision. **Third TMA event occurred after primary analysis data cutoff; 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 patient tested positive for anti-drug antibodies.

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

TMA=Thrombotic microangiopathy; aPCC=Activated prothrombin complex concentrate; rFVIIa=Activated recombinant FVII
*rFVIIa treatment in TMA #1 included treatment during resolution of the event. **Patient developed TMA following aPCC treatment for recurrent rectal hemorrhage after primary analysis data cutoff. Rectal hemorrhage eventually fatal, death was deemed unrelated to emicizumab. TMA laboratory values (platelets, LDH) showed evidence of improvement of TMA after aPCC discontinuation. Patient also received tranexamic acid.

Common characteristics of TMA/thrombotic events were high cumulative doses of aPCC

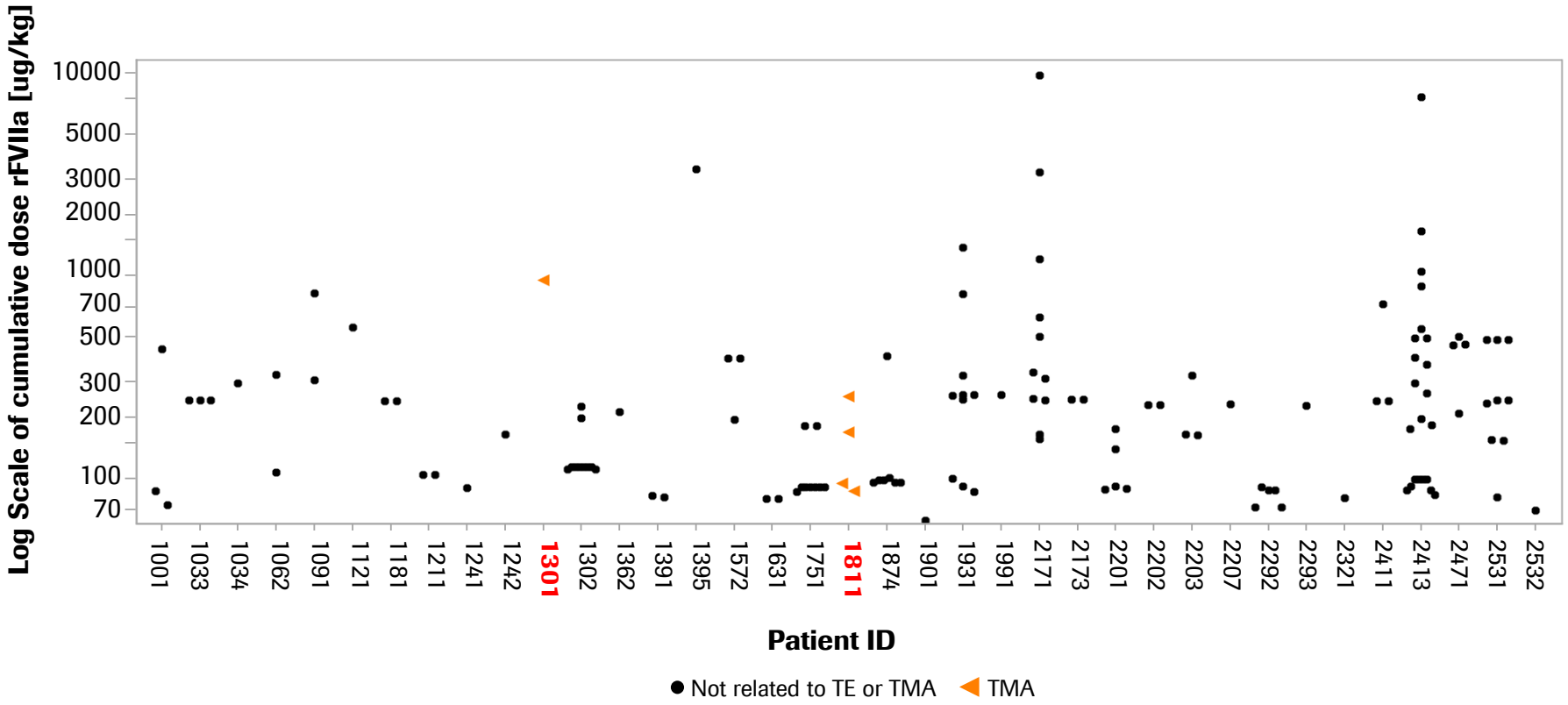


All TMA/thrombotic events were seen in cumulative doses of aPCC (>200 U/kg) for ≥24 hours

TMA=Thrombotic microangiopathy; TE=Thromboembolis; aPCC=Activated prothrombin complex concentrate

No TMA/thrombotic events occurred when only rFVIIa was used for breakthrough bleed treatment

Patients 1301 and 1811 received concurrent aPCC

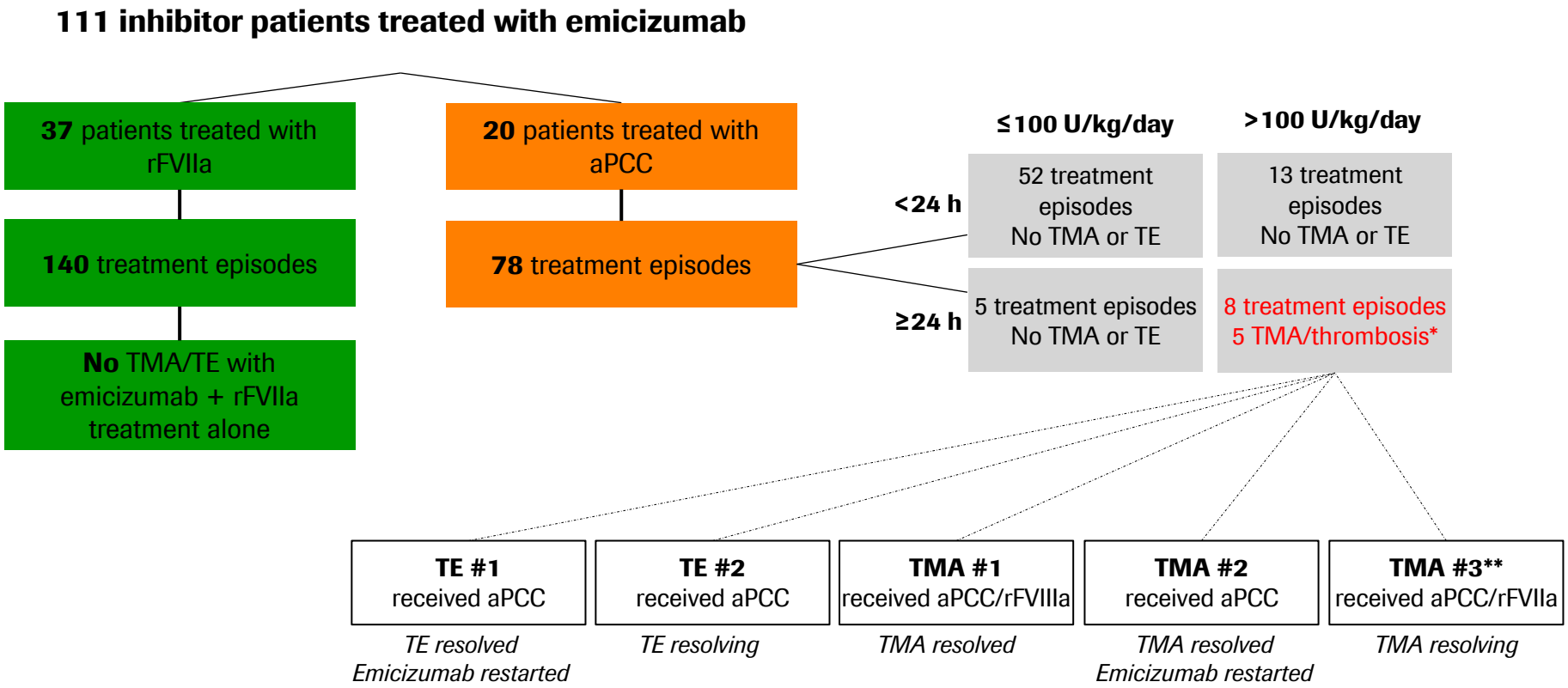


No TMA/thrombotic events occurred in patients taking only rFVIIa, despite very high doses in some cases

In patient 1811, some of the rFVIIa doses were administered while TMA was resolving.
TMA=Thrombotic microangiopathy; rFVIIa=Activated recombinant FVII; aPCC=Activated prothrombin complex concentrate

Interaction between emicizumab and aPCC

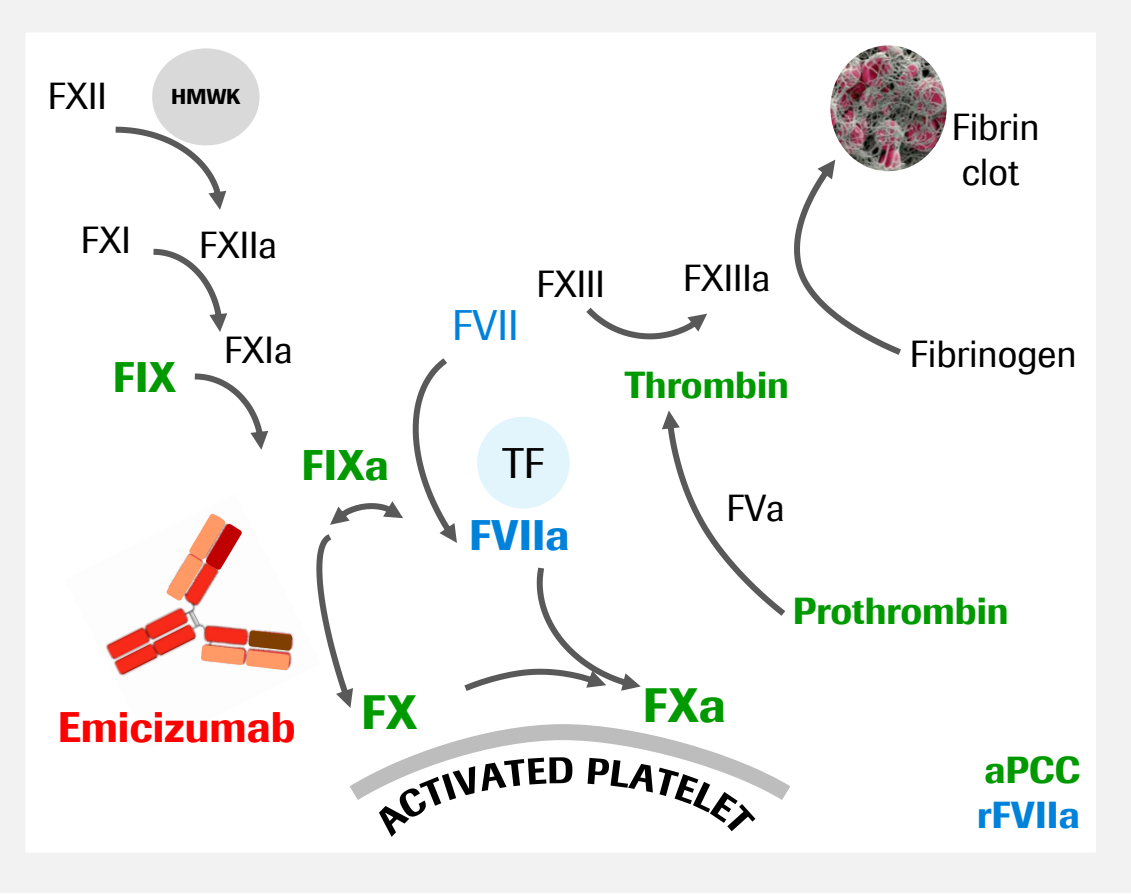
Five patients experienced TE or TMA



Risk of TMA/thrombotic events may be mitigated with BPA dosing guidance
No further events in >350 patients treated in emicizumab development program to date

TE=Thromboembolism; TMA=Thrombotic microangiopathy; aPCC=Activated prothrombin complex concentrate; BPA=Bypassing agent
*Two patients also received rFVIIa prior to/during the event. **Patient developed TMA following aPCC treatment for recurrent rectal hemorrhage after primary analysis data cutoff. Rectal hemorrhage eventually fatal, death was deemed unrelated to emicizumab. TMA laboratory values (platelets, LDH) showed evidence of improvement of TMA after aPCC discontinuation. Patient also received tranexamic acid.

Potential mechanism for combination effects of emicizumab with bypassing agents



aPCC characteristics[1]:

- Prothrombin, FVII, FIX and FX
- Low levels of thrombin, FIXa and FXa, FVIIa and FVIIIa
- Factor half life up to 65 hrs[2] leads to accumulation with repeated dosing

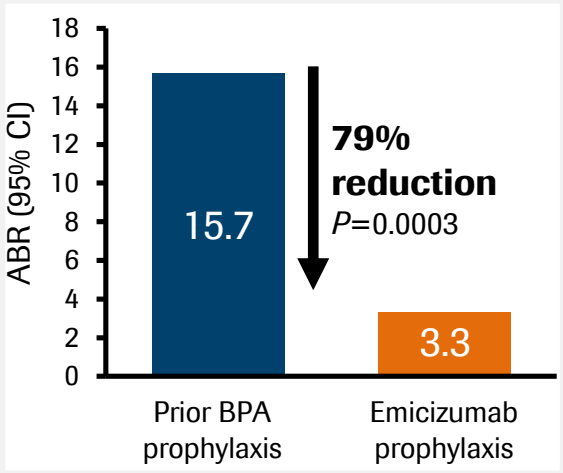
rFVIIa characteristics[3]:

- Recombinant activated FVII
- 2.3–6 hour half life[3]

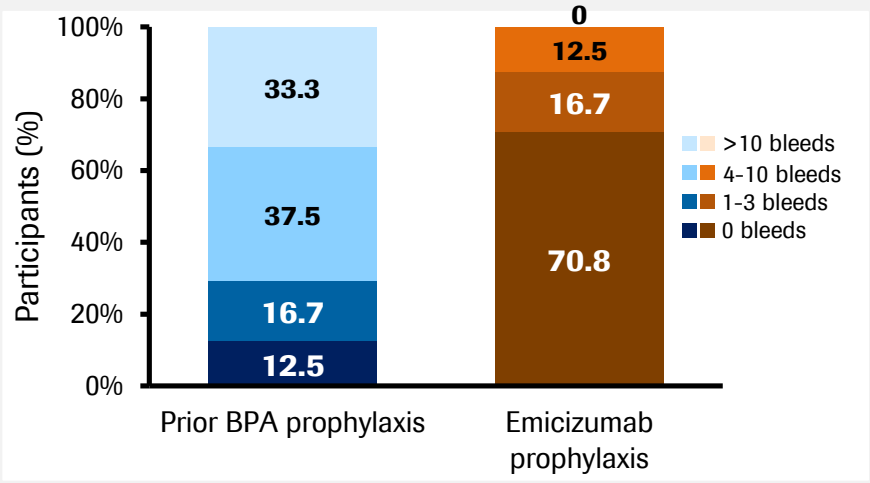
[1] FEIBA Summary of Product Characteristics, Baxter, 2013; [2] Hoffbrand & Moss Essential Hematology, 6th ed., 2011;
[3] NovoSeven Summary of Product Characteristics, Novo Nordisk

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

Bleed reduction



Categorized number of treated bleeds



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.

[1] Intra-individual comparison for 24 patients from NIS who had been on HAVEN1, Arm C
*Of 7 patients experiencing bleeds, 5 had reduced bleed rate compared to prior BPA prophylaxis; Primary analysis data cutoff – October 25, 2016
Median efficacy period: Prior BPA prophylaxis, 32 weeks; emicizumab prophylaxis, 30 weeks; ABR calculated with negative binomial regression model.
Median ABR calculated by number of bleeds/duration of efficacy period in days*365.25.
ABR=Annualized bleeding rate; BPA=Bypassing agent; NIS=Non-interventional study

Aspects of disease management

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HAVEN2: Ph3 interim data of emicizumab (ACE910) in pediatrics with hemophilia A with inhibitors

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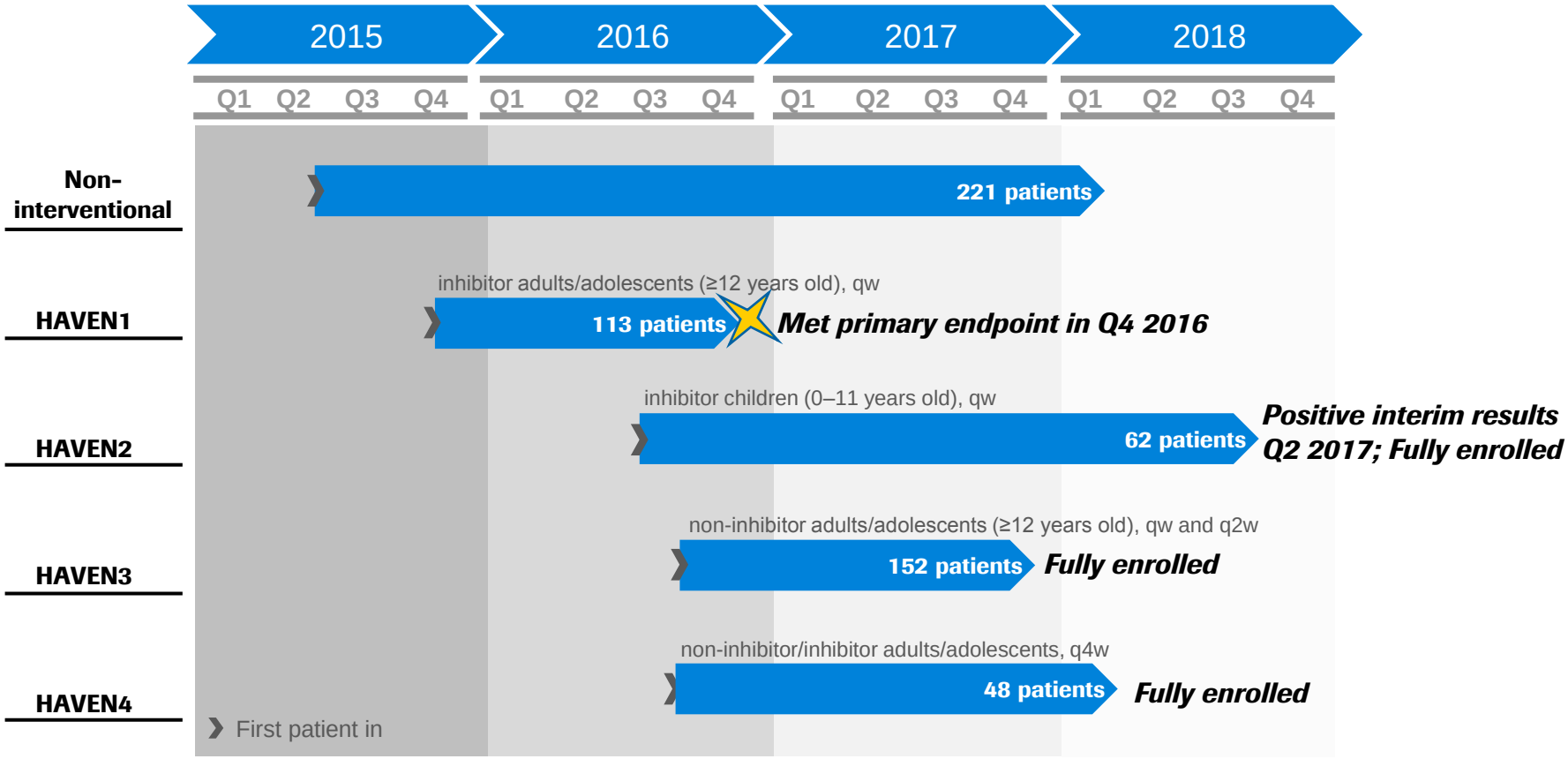
Emicizumab global development program

Emicizumab's phase III clinical development plan covers entire hemophilia A patient population



HAVEN1 and HAVEN2 filed in US and EU

Status of studies as of July 10, 2017

Doing now what patients need next