

# Pharmacodynamic data and coagulation biomarkers in persons with hemophilia A with inhibitors: results from the HAVEN 1 emicizumab phase 3 study

**Joanne I. Adamkewicz<sup>1</sup>, Christophe Schmitt<sup>2</sup>, Andreas Calatzis<sup>3</sup>, Guy Young<sup>4</sup>, Claude Negrier<sup>5</sup>, Michael Callaghan<sup>6</sup>, Jeffrey M. Venstrom<sup>1</sup>, Elina Asikanius<sup>2</sup>, Gallia Levy<sup>1</sup>, Benjamin Kim<sup>1</sup>**

<sup>1</sup>Genentech, Inc., South San Francisco, CA, USA; <sup>2</sup>F. Hoffmann-La Roche Ltd, Basel, Switzerland; <sup>3</sup>Roche Diagnostics International Ltd., Rotkreuz, Switzerland;

<sup>4</sup>Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA, USA;

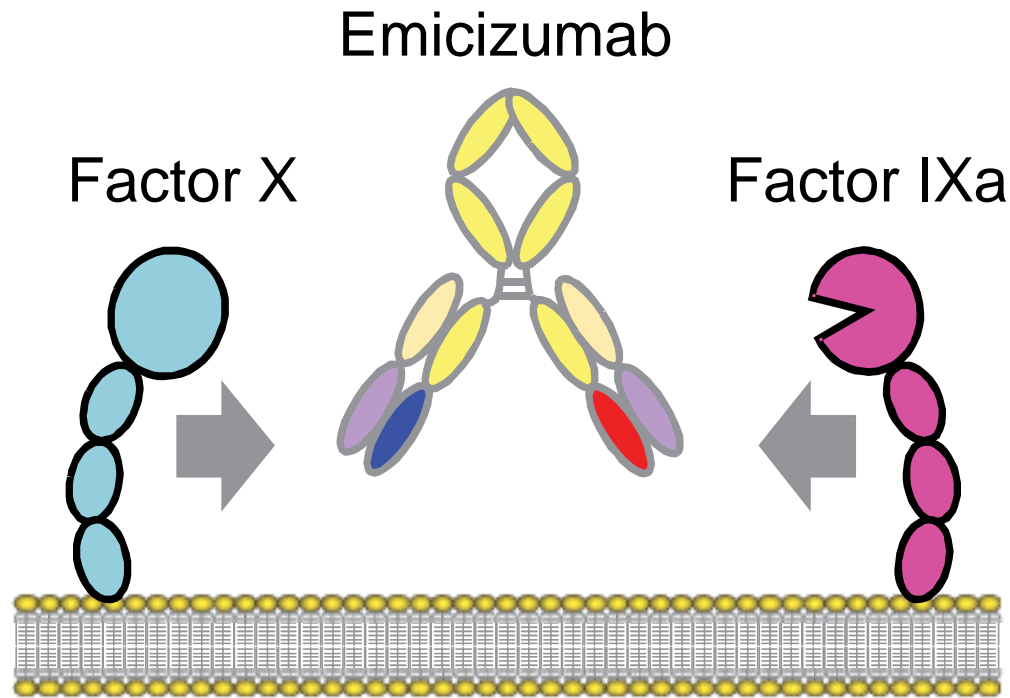
<sup>5</sup>Louis Pradel University Hospital, Lyon, France; <sup>6</sup>Children's Hospital of Michigan, Detroit, MI, USA

# Disclosures

Joanne I. Adamkewicz is an employee of Genentech, Inc.

# Emicizumab (ACE910)

## Humanized bispecific monoclonal antibody



- Bridges activated FIX (FIXa) and FX to restore function of missing activated FVIII required for effective hemostasis<sup>1,2</sup>
- Unique structure – not expected to induce FVIII inhibitors or be affected by presence of inhibitors<sup>2</sup>
- Long half-life (4–5 weeks) and administered subcutaneously<sup>3,4</sup>
- HAVEN 1: a randomized phase 3 study in adults and adolescents with hemophilia A with inhibitors against FVIII (N=109)
  - Weekly emicizumab prophylaxis resulted in a significant decrease in bleeding events compared with episodic or prior prophylactic bypassing agents (Oldenburg et al, ISTH 2017, Abstract ASY 01.1)
  - Majority of participants (62.9%) randomized to emicizumab prophylaxis had zero bleeds

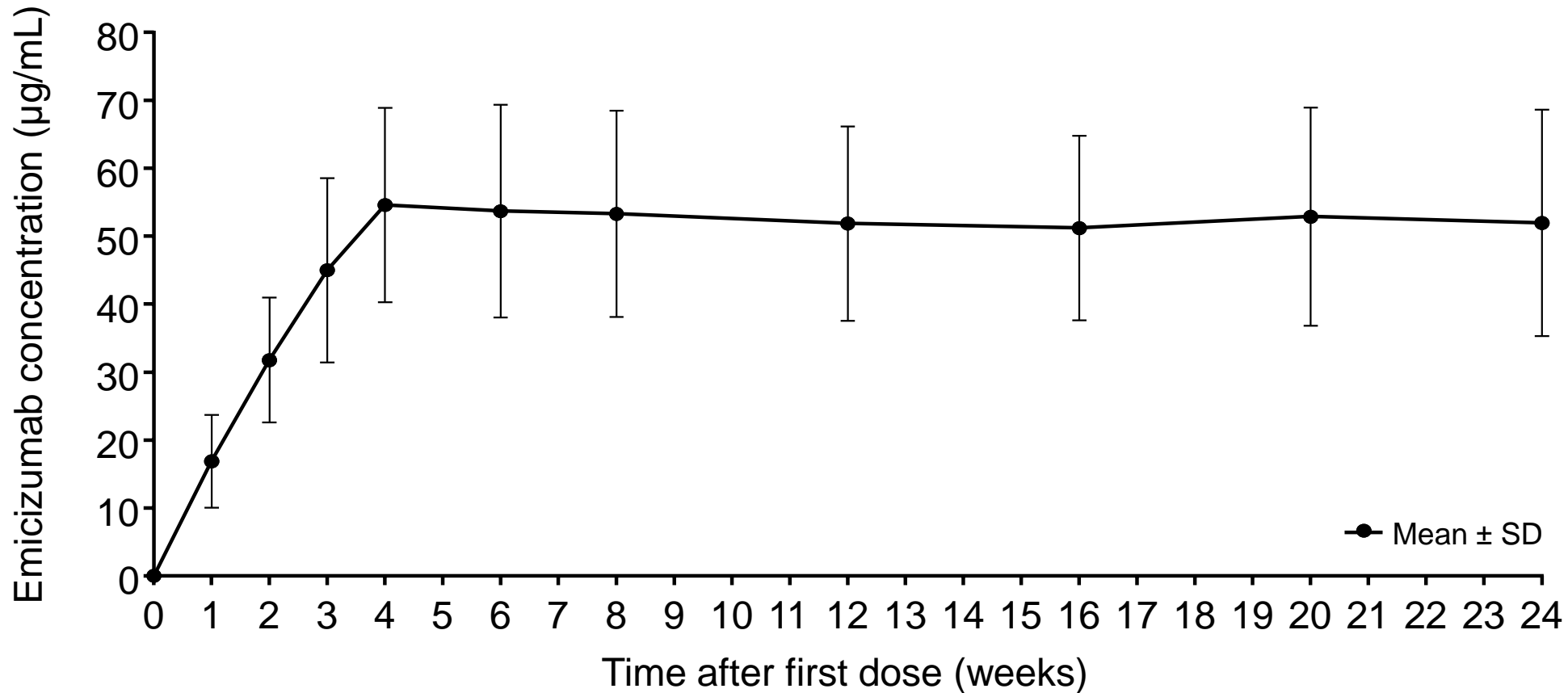
1. Kitazawa T, et al. *Nat Med* 2012;18:1570–4.  
2. Sampei Z, et al. *PLoS One* 2013;8:e57479.

3. Uchida N, et al. *Blood* 2016;127:1633–41.  
4. Shima S, et al. *N Engl J Med* 2016;374:2044–53.

# HAVEN 1 biomarker-related exploratory objectives

- To evaluate the pharmacodynamic effects of emicizumab in HAVEN 1
- To determine best practices for laboratory monitoring of emicizumab

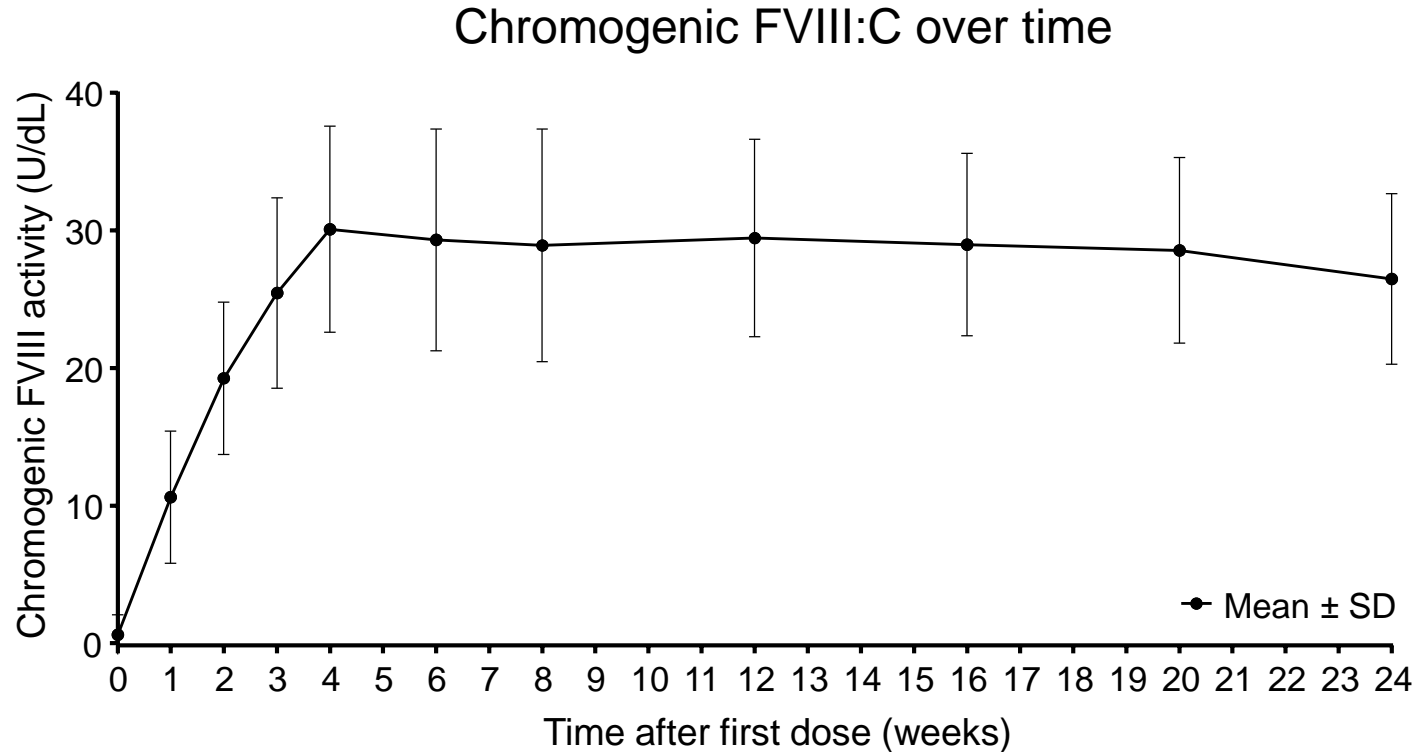
# HAVEN 1 pharmacokinetics – mean trough emicizumab plasma concentrations of $>50 \mu\text{g/mL}$ were achieved and sustained



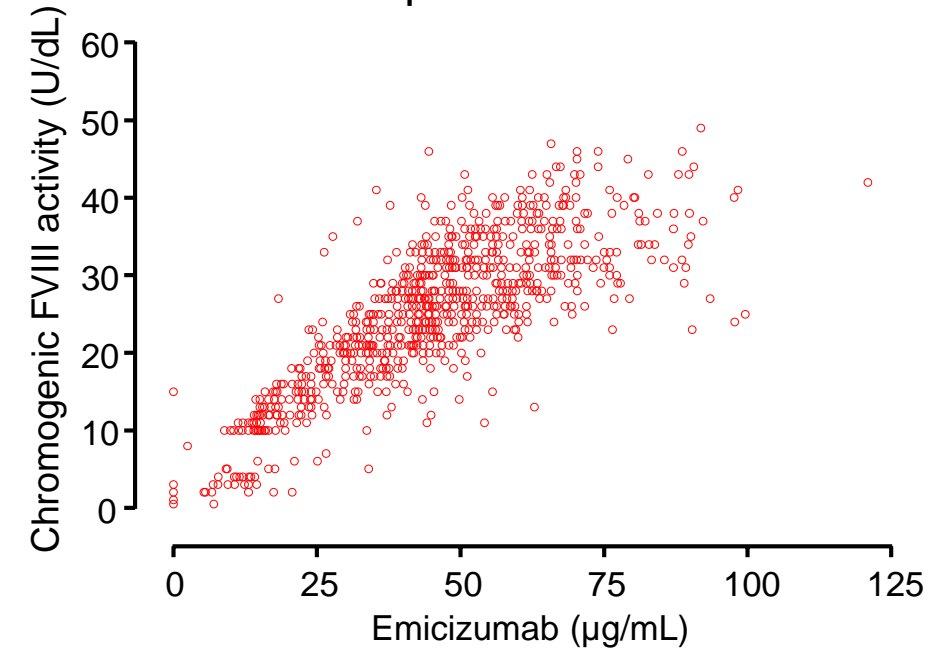
Patients, n: 101 99 102 99 98 93 82 70 60 54 49

- Four loading doses of 3 mg/kg/week followed by maintenance doses of 1.5 mg/kg/week; subcutaneous injection

# Emicizumab drives a concentration-dependent increase in reported FVIII activity that is sustained over time



Chromogenic FVIII:C vs. emicizumab plasma concentration



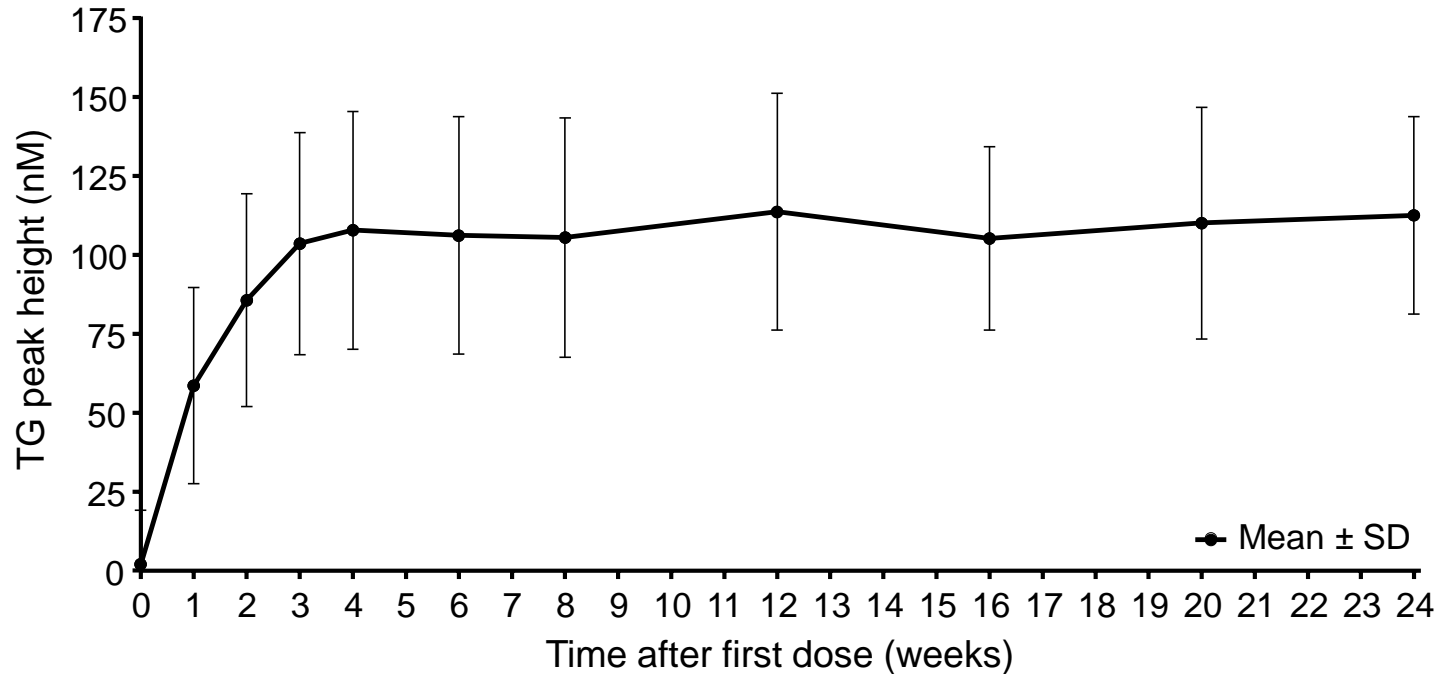
Patients, n: 103 102 102 102 101 97 86 72 60 56 50

- A commercial assay containing **human** FIXa and FX was used (Hyphen Biophen FVIII:C)
  - Emicizumab does not drive activity in chromogenic tests that use **bovine** factors (all other kits on market)
- Emicizumab and FVIIIa co-factor properties are not identical; thus, reported FVIII:C is an approximation of emicizumab hemostatic activity. Nevertheless, it provides a relative indication of the pro-coagulant activity of emicizumab

Red dots represent individual patients (N=102), each with multiple assessments over time (931 total data points).

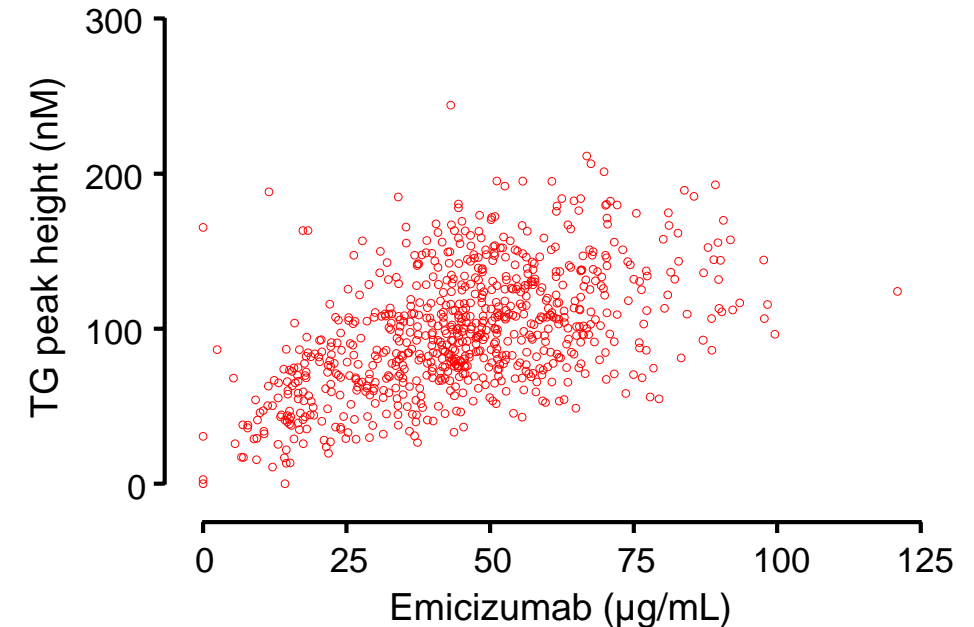
# Emicizumab drives a concentration-dependent increase in thrombin generation (TG) that is sustained over time

TG peak height over time



Patients, n: 95 94 95 93 92 86 79 64 52 50 44

TG peak height vs. emicizumab plasma concentration

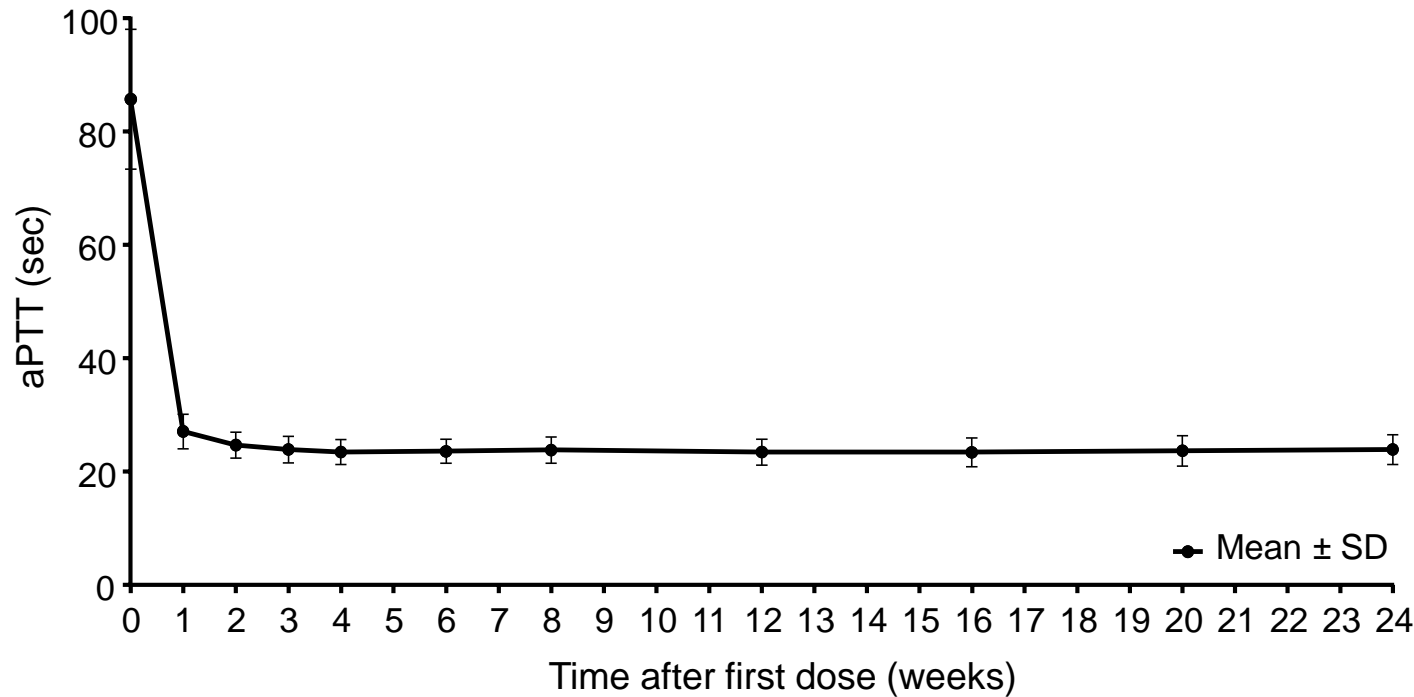


- Thrombin generation test with FXIa trigger in platelet-poor citrate plasma
- Mean peak height was roughly equivalent to 30% of normal pooled plasma in this assay

Red dots represent individual patients (N=95), each with multiple assessments over time (844 total data points).

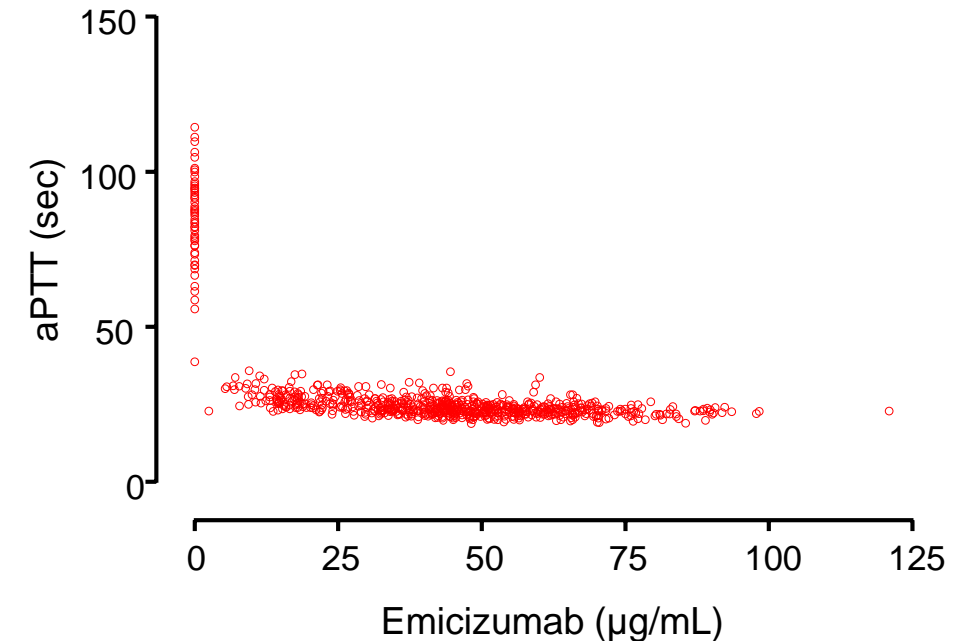
# Emicizumab has a very strong in vitro effect on aPTT: unlike FVIII, it does not require an activation step

aPTT over time



Patients, n: 91 95 96 95 94 90 79 65 54 51 46

aPTT vs. emicizumab plasma concentration



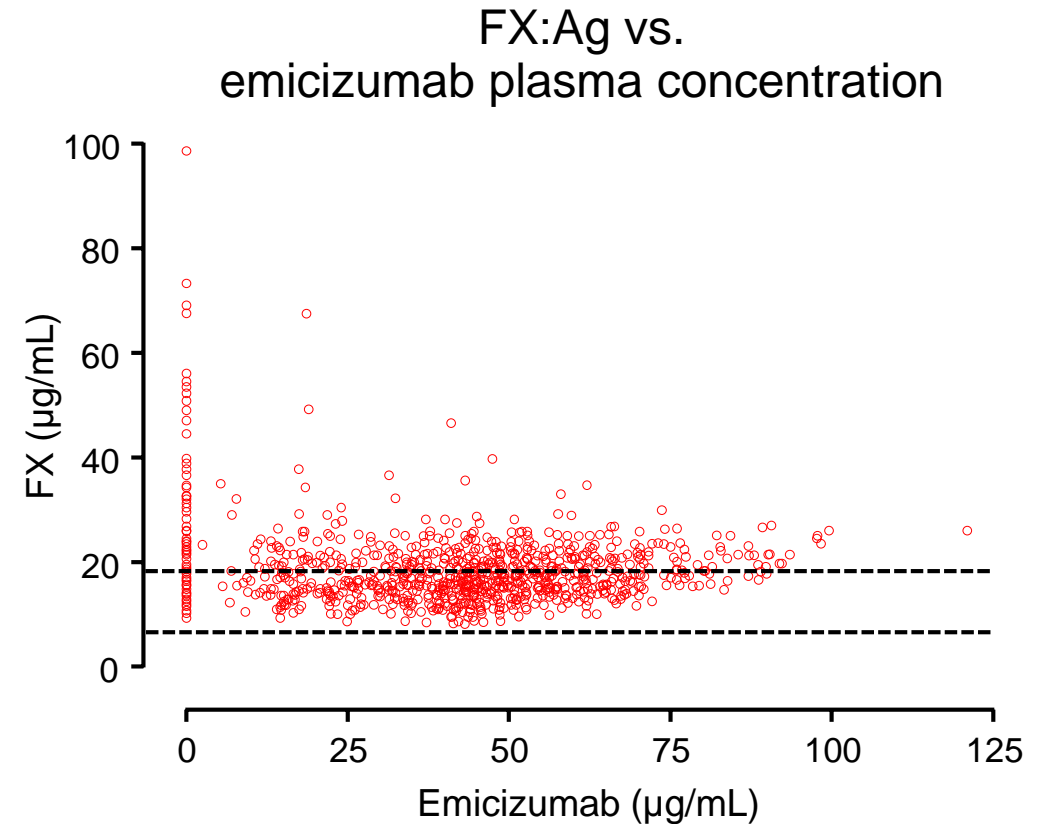
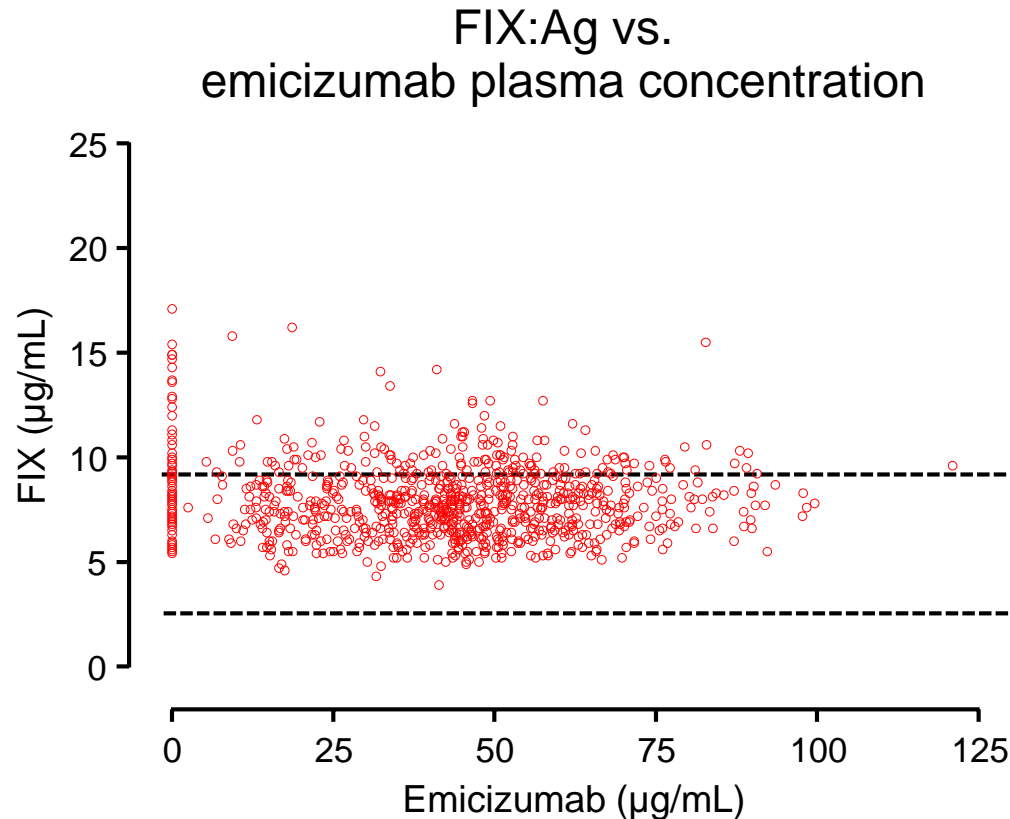
- In assays of intrinsic clotting time, emicizumab behaves like FVIIIa, not FVIII
- aPTT is not an accurate measure of hemostatic potential in the presence of emicizumab
- Chromogenic or immuno-based methods provide an alternative to intrinsic clotting-based methods<sup>1</sup>

Red dots represent individual patients (N=96), each with multiple assessments over time (856 total data points).

1. Adamkewicz JI, et al. *Intl Lab Hem* 2017;39(Suppl 2):24.



# Concentrations of FIX and FX antigens, the binding targets of emicizumab, are stable during emicizumab treatment

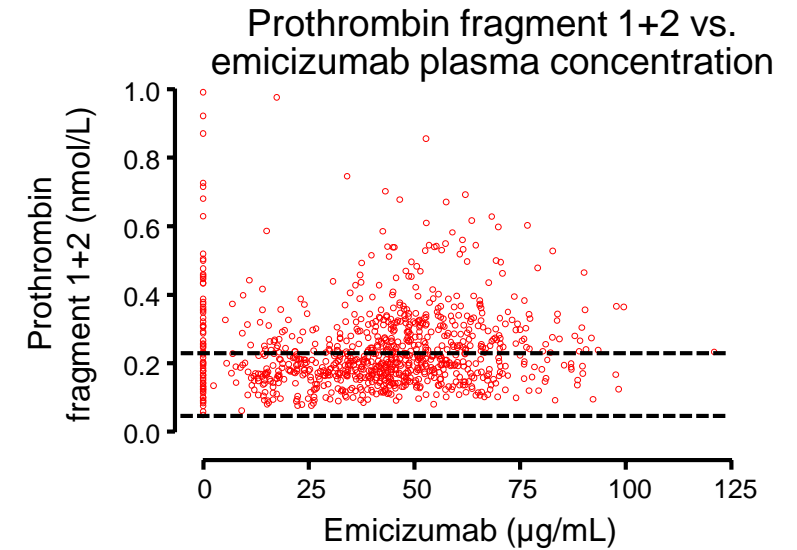
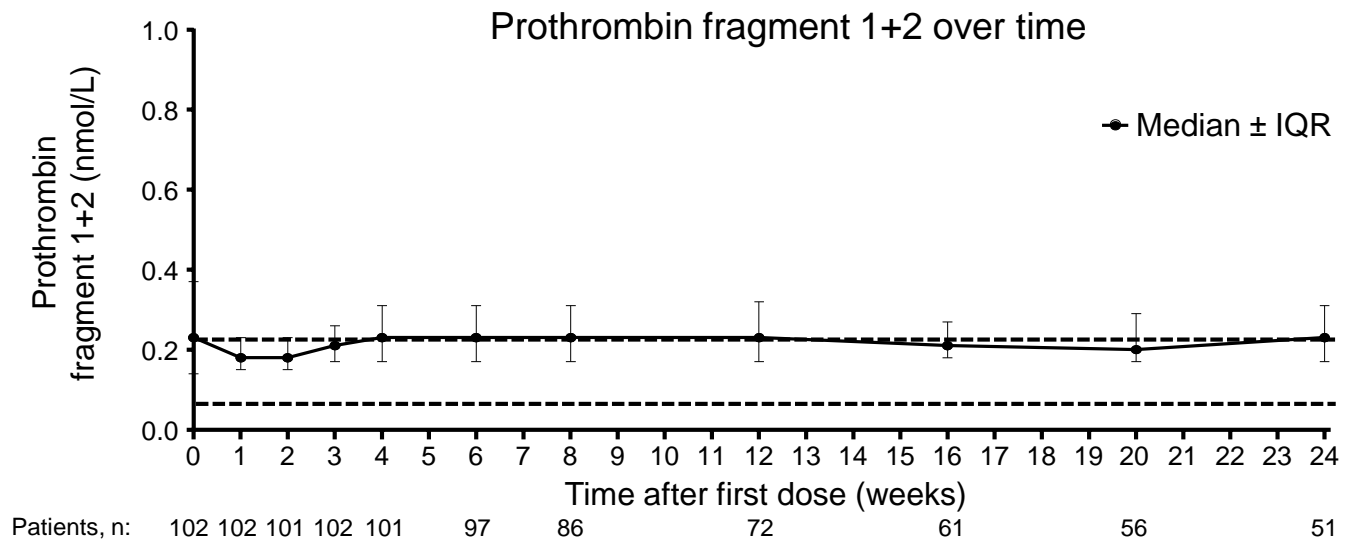
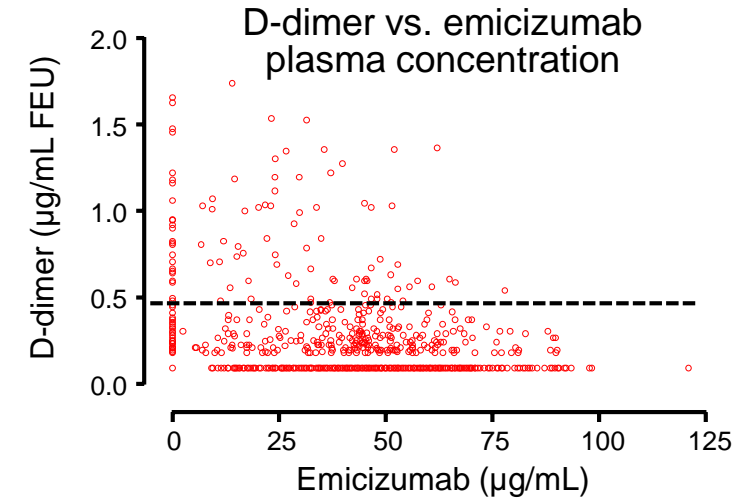
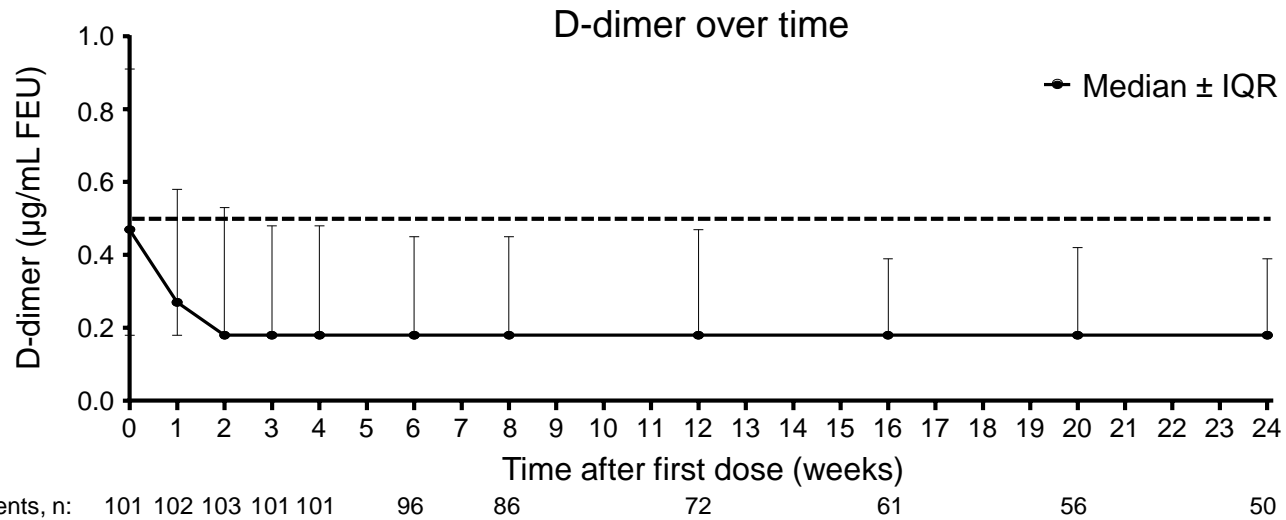


- Higher baseline values may reflect accumulation of FIX and FX due to prior aPCC use as these factors have a half-life of 25 and 40 hours, respectively<sup>1</sup>
- No changes seen for PT/INR, vWF:Ag, or fibrinogen (data not shown)

Dotted lines indicate laboratory-determined reference range using research-grade ELISA; no clinical IVD test is available and no established normal reference range exists for these antigens. aPCC, activated prothrombin complex concentrate; PT/INR, prothrombin time/international normalized ratio; vWF, von Willebrand factor.

1. Hoffbrand & Moss Essential Haematology, 6th ed. 2011.

# Markers of activated coagulation are not elevated during emicizumab treatment



Dotted lines represent normal reference ranges.  
FEU, fibrinogen equivalent units; IQR, interquartile range.

# Conclusions

- Emicizumab showed the desired pro-coagulant effect with sustained, concentration-dependent activity as measured by FVIII:C and thrombin generation
- Other aspects of the coagulation cascade were unperturbed (PT/INR, FIX:Ag, FX:Ag, vWF:Ag)
- No evidence of hypercoagulation was seen (D-dimer, prothrombin fragment 1+2)
- Laboratory monitoring practices should be adjusted for patients receiving emicizumab
  - aPTT results must be interpreted with knowledge of pharmacodynamic effect, as normal aPTT does not imply normal capacity for coagulation
    - Due to its mechanism of action, intrinsic clotting times are shortened with emicizumab
  - Chromogenic FVIII determination is sensitive to emicizumab when human FIXa and FX are utilized (Hyphen Biophen FVIII:C)
  - Chromogenic Bethesda Assay should be used for measurement of FVIII inhibitor titer (Adamkewicz et al, ISTH 2017, Poster PB 954)

**Biomarker results in HAVEN 1 are consistent with the safety, efficacy, and pharmacokinetic profile of emicizumab prophylaxis**

# Acknowledgements

- The authors would like to thank:
  - Study participants and their families
  - Study investigators and site personnel:

S. Bonanad Boix (Spain), W. Bujan (Costa Rica), M. Callaghan (USA), G. Castaman (Italy), P. Collins (UK), S. Croteau (USA), G. Dolan (UK), M. Escobar (USA), C. Escuriola-Ettingshausen (Germany), E. Eyster (USA), T. Fujii (Japan), K. Fukutake (Japan), A. Hellman (Poland), K. Holstein (Germany), V. Jimenez-Yuste (Spain), D. Keeling (UK), C. Kempton (USA), L. Khoo (Australia), J. Kim (Republic of Korea), R. Kruse-Jarres (USA), T. Lambert (France), J. Mahlangu (South Africa), T. Matsushita (Japan), C. McGuinn (USA), C. Negrier (France), R. Nuñez (Spain), P. Ockelford (New Zealand), J. Oldenburg (Germany), D. Quon (USA), M. Recht (USA), C. Rothschild (France), E. Santagostino (Italy), T. Sato (Japan), M. Shima (Japan), S. Susen (France), M. Taki (Japan), H. Tran (Australia), W. Tsay (Taiwan), M. Wang (USA), J. Windyga (Poland), T. Wozny (Poland), G. Young (USA)
  - Chugai, Roche, and Genentech teams
  - Medpace Reference Laboratories, Cincinnati, OH, USA
- This study was co-sponsored by F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co., Ltd
- Editorial assistance was provided by Daniella Babu, PhD, Envision Pharma Group, and funded by F. Hoffmann-La Roche Ltd

*Thank you*

