NOVES LÍNIES DE FÀRMACS EN EL TRACTAMENT DE LA HEMOFILIA A

Terapias Disruptivas

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CONFLICTOS DE INTERESES

- Consultor : Bayer , Takeda, Novo-Nordisk
- Conferenciante : Octapharma , Bayer, Novo-Nordisk, Roche, Takeda

Tratamientos Disruptivos (Wikipedia)

Tecnología disruptiva o innovación disruptiva es aquella tecnología o innovación que conduce a la aparición de productos y servicios que utilizan preferiblemente una estrategia disruptiva (de disruptivo, '**que produce ruptura brusca**') frente a una estrategia sostenible a fin de competir contra una tecnología dominante, buscando una progresiva consolidación en un mercado. Aunque inicialmente el término proviene de la economía, actualmente comienza a tener mucha importancia a la hora de plantear estrategias de desarrollo en los departamentos de I+D de muchas compañías

La conducta disruptiva "se caracteriza por una ruptura muy marcada respecto a las pautas de conducta y valores generales o sociales aceptados, que pueden amenazar la armonía e incluso la supervivencia del grupo a través de acciones hostiles y provocadoras que incitan a la desorganización de las actividades interpersonales y grupales

Evolución del tratamiento en Hemofilia

2nd Century AD……

Fresh whole blood

Citrated plasma

Fractionated and fresh-frozen plasma

Cryo-precipitate

aPCC

Heat-treated FVIII/IX concentrates

rFVIIa

Enhanced viral inactivation methods inc. Mab technology

Recombinant FVIII/IX products Hamster-cell lines

Longer-acting recombinant FVIII/IX products and HEK-cell line derived FVIII

1840 ---- 1930 1940 1950 1960 1970 1980 1990 2000 2010 2020

Haemophilia A and B identified

Home treatment

Comprehensive care centers

F9 and *F8* genes sequenced

HIV and hepatitis epidemic

Prophylaxis established

Non-replacement principles

Gene therapy

Kingdon et al .

Nuevas Terapias en Hemofilia

- Con Factor VIII
- Factor VIII r de origen humano
- Factores VIII r Pegilados
- Factor VIII r proteínas de fusión / cadena única
- Factor VIII r via subcutánea

- Sin Factor VIII
- Anticuerpo mimético
- Inhibición de la Antitrombina
- Inhibición de TFPI
- Terapia Génica

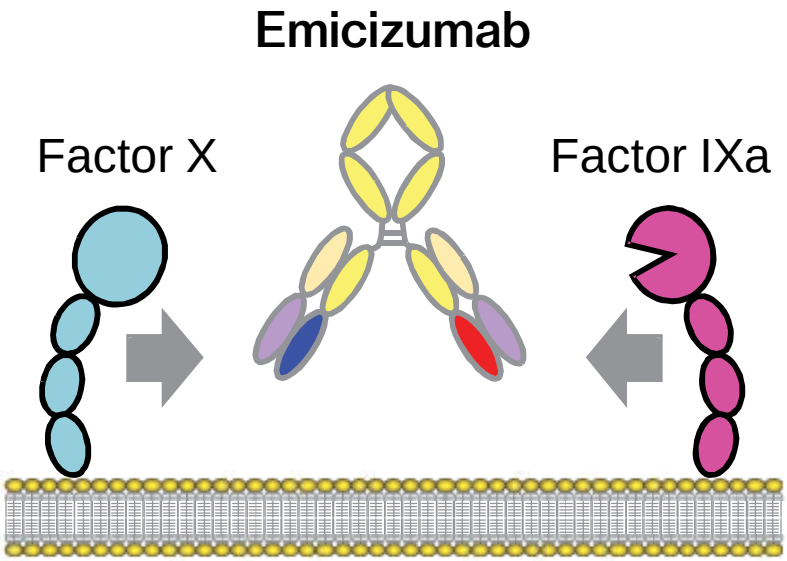
Tratamientos Disruptivos en Hemofilia A

Product (generic name)	Manufacturer	Mechanism of action	Clinical trial status	Reference
ACE 910 (emicizumab)	Chugai/ Hoffman-La Roche (Basel, Switzerland)	Humanized bispecific monoclonal antibody, mimics FVIII	Phase III	Shima *et al.*,[81] Uchida *et al.*,[82] Oldenburg *et al.*[83]
NN-7415 (concizumab)	Novo Nordisk (Copenhagen, Denmark)	Humanized monoclonal antibody against TFPI	Phase I	Mancuso and Santagostino,[44] Chowdary *et al.*[84]
BAY 1093884	Bayer (Berlin, Germany)	Humanized monoclonal antibody against TFPI	Phase I	Monahan *et al.*,[85] Gu *et al.*[86]
ALT-AT3 (fitusiran)	Alnylam (Cambridge, Germany)	siRNA against AT3	Phase I/II	Sehgal *et al.*,[87] Pasi *et al.*,[88] Monahan,[89] Pasi *et al.*[90]

FVIII factor VIII; TFPI, tissue factor pathway inhibitor.

Balkaransingh P et al Ther Adv Hematol 2018

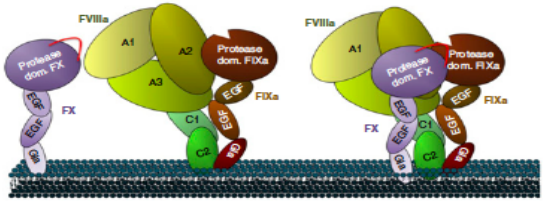
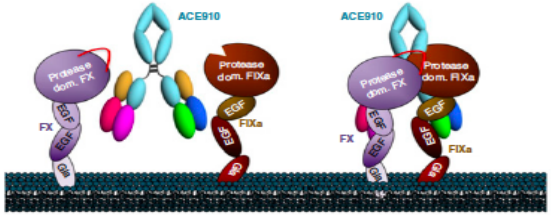
Background: Emicizumab



- Humanised bispecific monoclonal antibody
- Bridges activated factor IX (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 FVIII inhibitors)
- Long half-life of ~30 days
- Administered subcutaneously
- Approved in several countries for once-weekly prophylaxis in persons with haemophilia A with inhibitors of all ages

Oldenburg et al. N Engl J Med 2017

Factor VIIIa vs Emicizumab

FVIIIa	ACE910/Emicizumab
	
Multiple sites of interaction	Single sites of interaction
High affinity for enzyme & substrate *(low to high nanomolar range)*	Low affinity for enzyme & substrate *(micromolar range)*
Specific for FIXa and FX *(no binding to FIX and FXa)*	No distinction between zymogen and enzyme *(FIX vs FIXa and FX vs FXa)*
Full cofactor activity - *promotes phospholipid binding* - *stabilizes FIXa active site* - *bridges FIXa to FX*	Partial cofactor activity - *bridges FIXa to FX*
Enzyme and substrate are in excess over cofactor	Antibody is in excess over enzyme and substrate
FVIIIa has on/off mechanism	Emicizumab has no on/off mechanism
High level of self-regulation	Low level of self-regulation

Lenting P. Blood 2017

Emicizumab clinical trials

Clinical trial	Population	ABR, treated bleeds: emicizumab prophylaxis vs no prophylaxis	% patients with zero treated bleeds	ABR, treated bleeds: emicizumab prophylaxis vs prior prophylaxis in NIS
HAVEN 1 NCT02622321	PwHA ≥12 years with FVIII inhibitors	▪ 87% reduction (QW)*	▪ 63% (QW), 6% (no prophylaxis)	▪ 79% reduction with emicizumab QW vs prior BPA prophylaxis
HAVEN 2 NCT02795767	PwHA <12 years with FVIII inhibitors	▪ N/A(no comparator)	▪ 87% (QW)	▪ 99% reduction with emicizumab QW vs prior BPA prophylaxis
HAVEN 3 NCT02847637	PwHA ≥12 years without FVIII inhibitors	▪ 96% reduction (QW) ▪ 97% reduction (Q2W)	▪ 56% (QW), 60% (Q2W), 0% (no prophylaxis)	▪ 68% reduction with emicizumab QW vs prior FVIII prophylaxis
HAVEN 4 **NCT03020160**	**PwHA ≥12 years with or without FVIII inhibitors**	▪ **Primary analyses evaluating emicizumab Q4W prophylaxis on bleeding rate, safety, PK**		

*Improved bleeding rate observed in subsequent 24-week periods beyond initial 24-weeks.

Oldenburg J, et al. *N Engl J Med* 2017;377:809–18.
Mancuso, ME, et al. *Blood* 2017;130:1071.
Young G, et al. *Blood* 2017;130:85.

Genentech Press Release. Nov 19, 2017.
Mahlangu J, et al. Presented at WFH 2018. Abstract 854.

ABR, annualized bleeding rate; BPA, bypassing agent; PwHA, persons with Haemophilia A; PK, pharmacokinetics; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, once weekly.

The NEW ENGLAND JOURNAL of MEDICINE

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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.

CONCLUSIONS

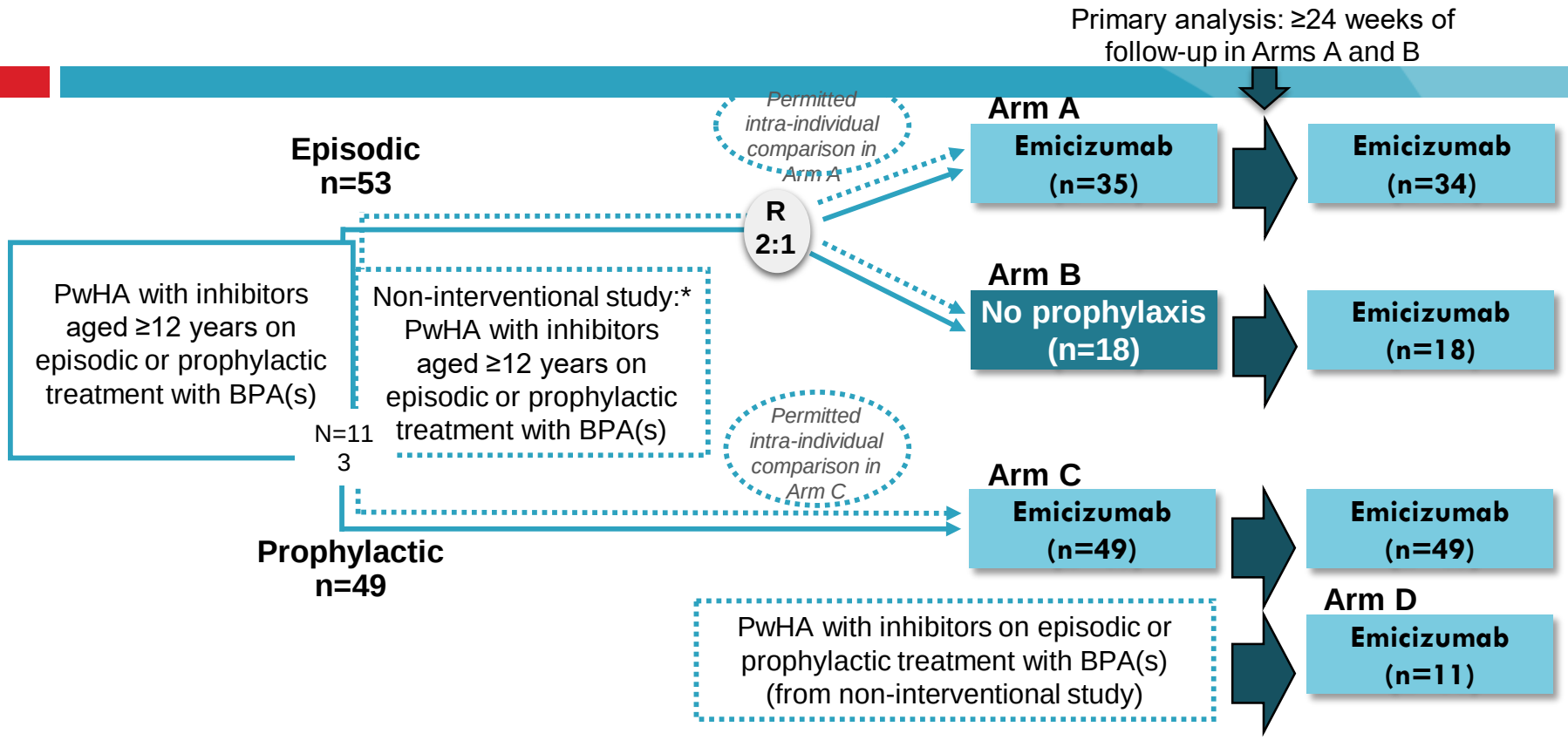
Emicizumab prophylaxis was associated with a significantly lower rate of bleeding events than no prophylaxis among participants with hemophilia A with inhibitors. (Funded by F. Hoffmann–La Roche and Chugai Pharmaceutical; HAVEN 1 ClinicalTrials .gov number, NCT02622321.)

Hipótesis del trabajo Haven1

PwHA with inhibitors are at risk of increased morbidity and have had limited treatment options.

Bleeding can be managed by prophylactic or episodic use of BPAs, but these agents have limitations:

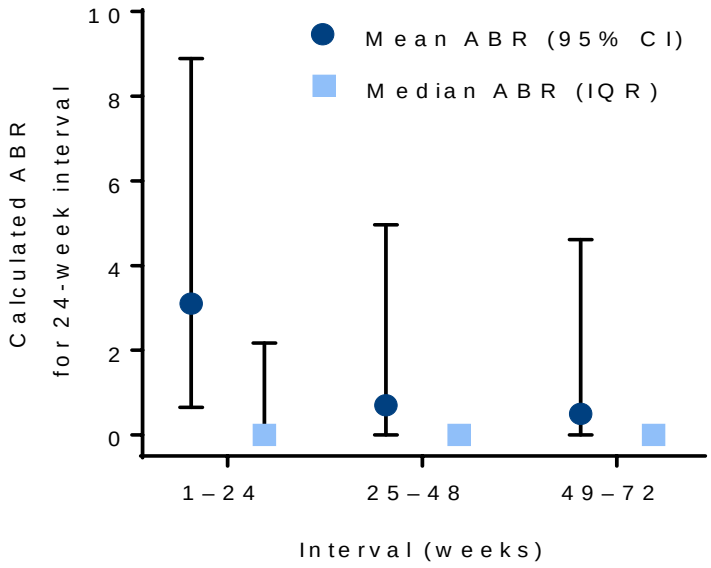
- More costly and less effective than FVIII replacement in PwHA without inhibitors
- Require frequent infusions, which add substantial treatment burden to PwHA with inhibitors



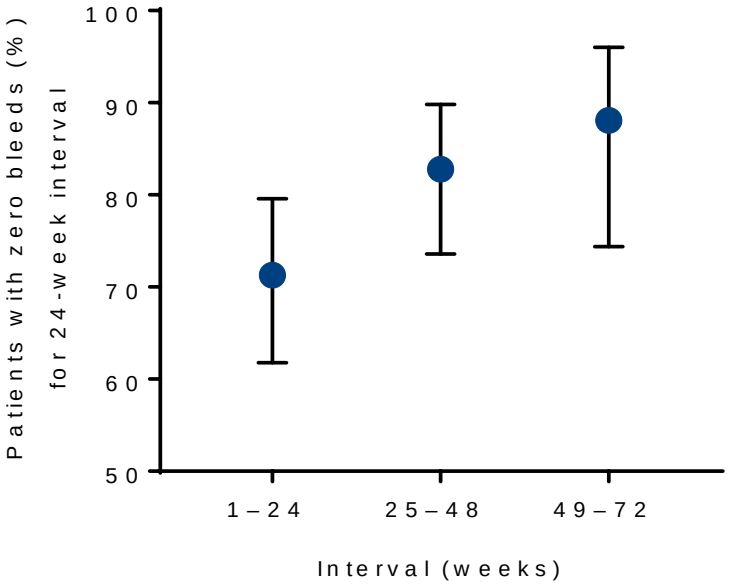
HAVEN 1: NCT02622321. *Non-interventional study: NCT02476942.
BPA, bypassing agent; PwHA, persons with haemophilia A; R, randomisation.

Total Emicizumab-Treated Patient *Bleeding Rates over Time on Emicizumab*

Annualised bleeding rates over 24-week intervals

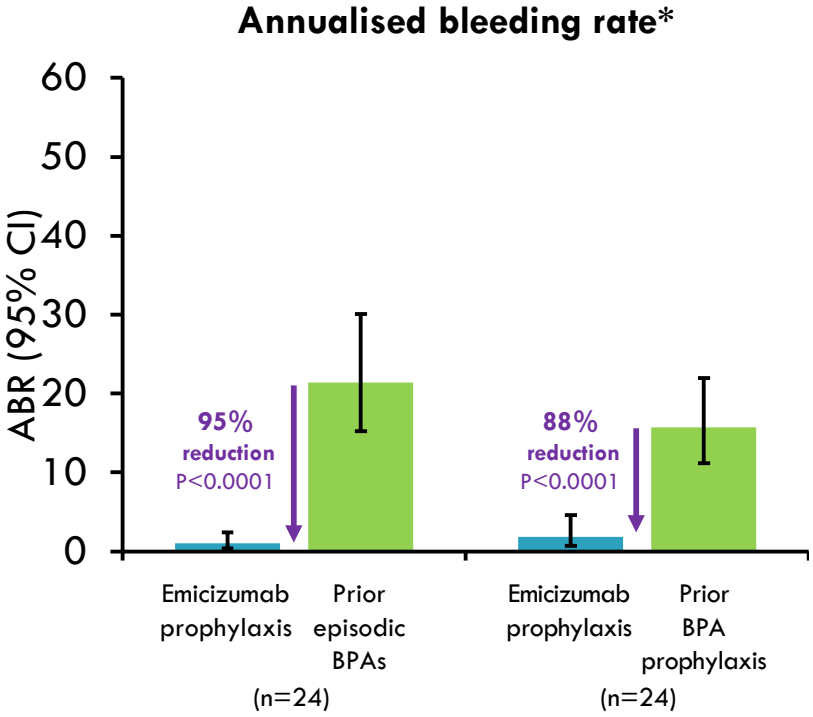


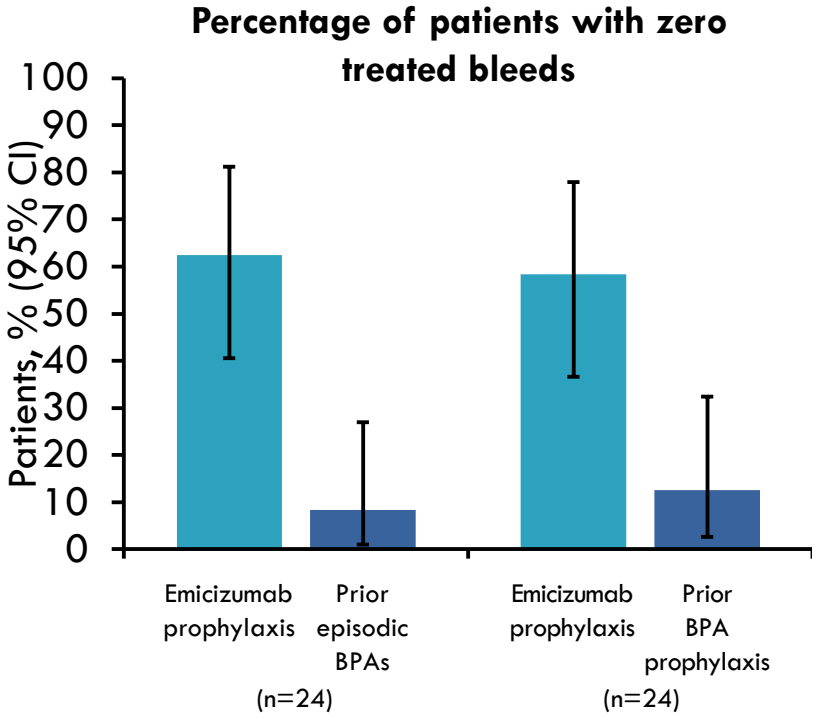
Patients with zero treated bleeds over 24-week intervals



ABR, annualised bleeding rate.

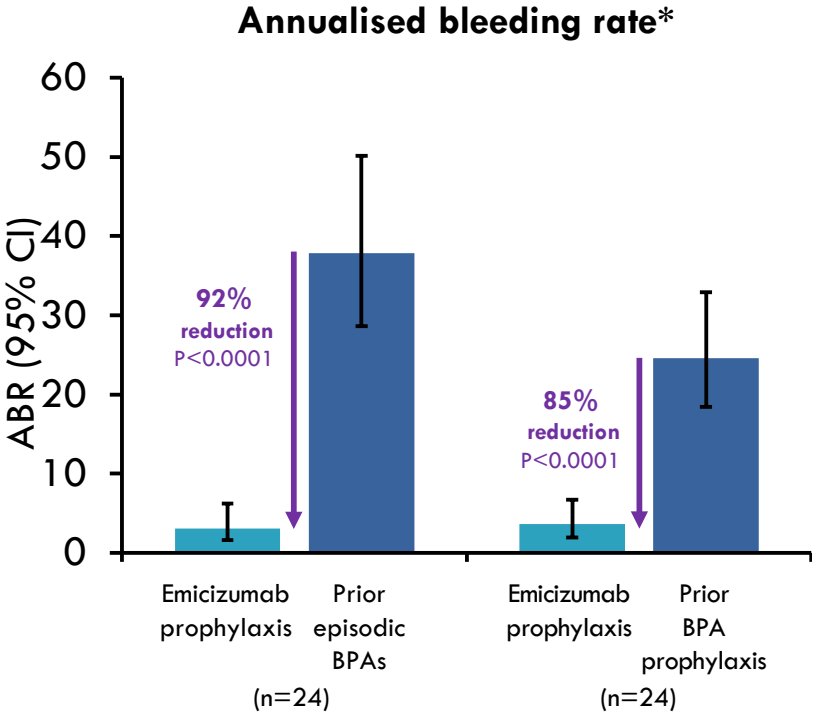
Intra-individual Comparisons: *Emicizumab Prophylaxis vs Prior BPA*

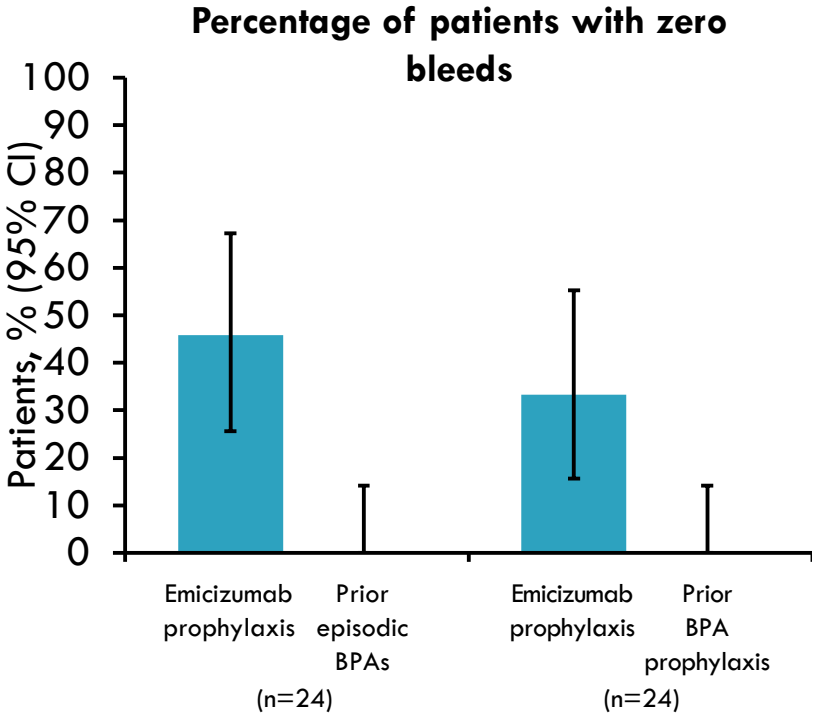




*Negative binomial regression model.
ABR, annualised bleeding rate; BPA, bypassing agent.

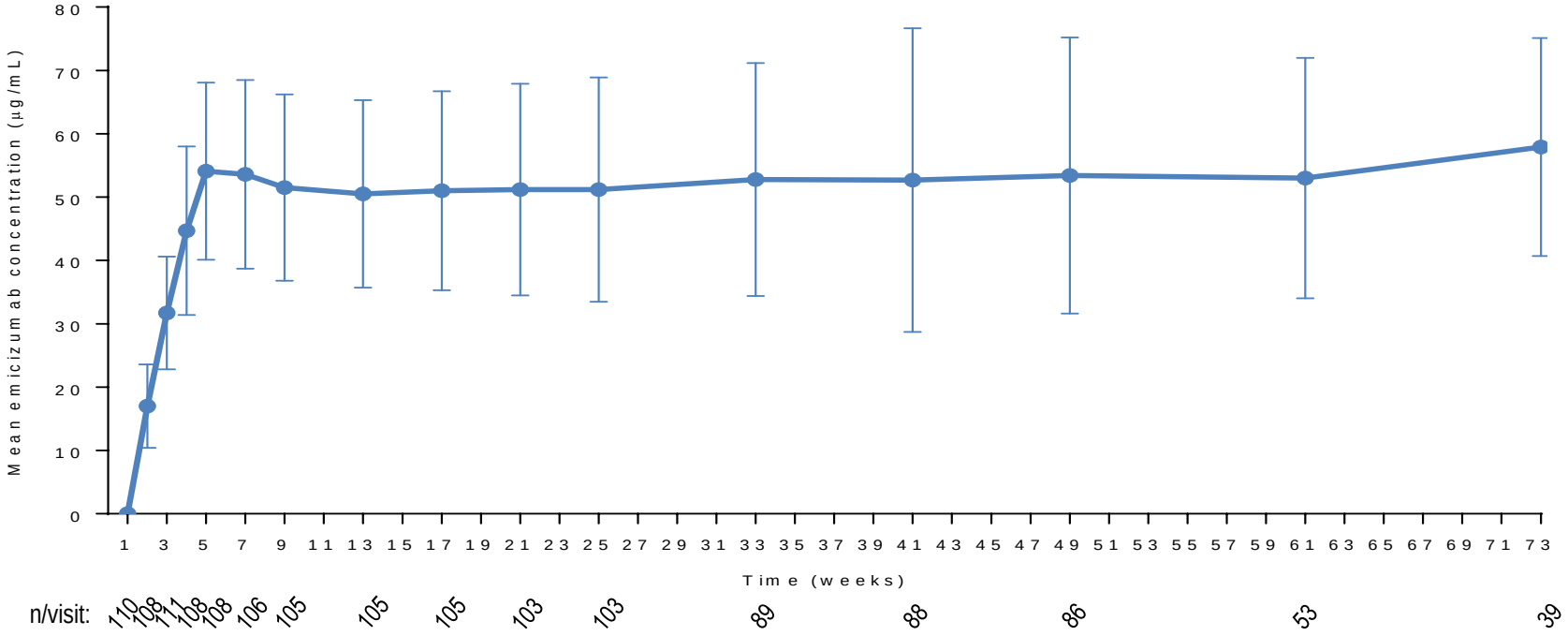
Intra-individual Comparisons: *Emicizumab Prophylaxis vs Prior BPA*





*Negative binomial regression model.
ABR, annualised bleeding rate; BPA, bypassing agent.

Mean Trough Emicizumab Plasma



CONCLUSIONES HAVEN-1

- En los pacientes con Emicizumab se demuestra una reducción significativa de los sangrados , en pacientes en profilaxis con BPA
- El ABR mejora de 3.1 a 0.5
- El % de pacientes con sangrados “cero”mejora a lo largo de 24 semanas hasta el 88%
- Los casos de MAT se asociaron a dosis altas de BPA

HAVEN 2 STUDY DESING : PHASE 3. MULTICENTER.INTERNATIONAL

- Paediatric PwHA with inhibitors aged ≥2 to <12 y (or 12–17 y if <40 kg)*
- All on episodic or prophylactic treatment with BPAs prior to study entry
- Enrolment aged <2 y permitted after interim analysis

Screening

Interim data reviews

Primary efficacy analysis
52 weeks after last patient enrolled

Weekly SC emicizumab prophylaxis
3 mg/kg/wk for 4 weeks; 1.5 mg/kg/wk thereafter

Potential individual efficacy-guided dose up-titration from week 12

24-week safety follow-up off study drug
OR
continue on emicizumab

*NCT02795767. Patients from non-interventional study (NCT02476942) (Cohort B) permitted to enrol.
BPA, bypassing agent; PwHA, persons with haemophilia A; SC, subcutaneous

HAVEN 2 Infants & Toddlers

	Emicizumab 1.5 mg/kg QW (N=10)
Sex, male, n (%)	10 (100.0)
Age	
min–max (months)	14.7−34.2
Haemophilia severity, n (%)	
Mild	0 (0)
Moderate	0 (0)
Severe	10 (100)
Previous ITI, n (%)	
Yes	2 (20)
No	8 (80)

	Emicizumab 1.5 mg/kg QW (N=10)
Prior BPA treatment, n (%)	
Episodic	2 (20)
Prophylactic	8 (80)
Weight (kg)	
min–max	9.5–14.8
Bleeds in prior 24 weeks	
Median (min–max)	6.0 (0–15)
Target joints, n (%)	
Yes	1 (10)
1	0
>1	1

BPA, bypassing agent; ITI, immune tolerance induction; QW, weekly

HAVEN 2 Infants & Toddlers

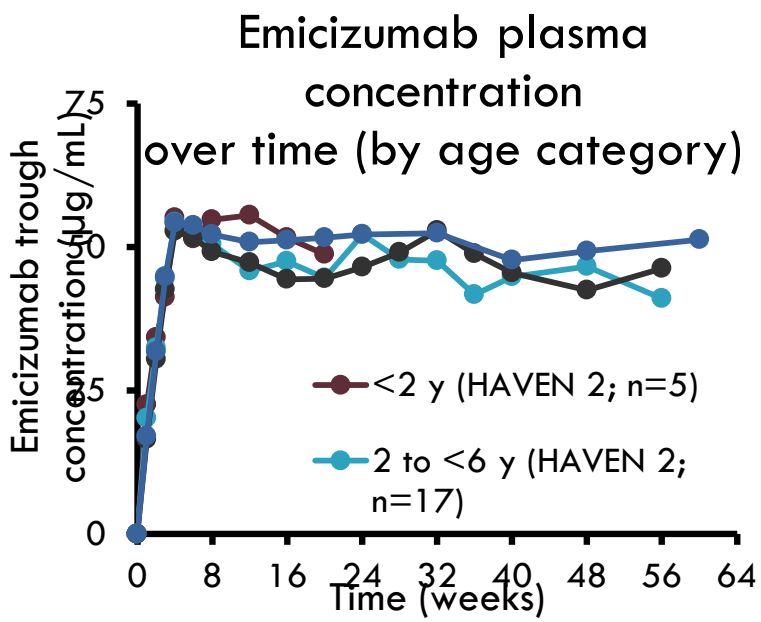
Adverse events (AEs)	Emicizumab 1.5 mg/kg QW (N=10)
Total patients with ≥1 AE, n (%)	7 (70)
Total number of AEs	19
Type of AE, n (%)	
Serious	0 (0)
Grade ≥3	0 (0)
Treatment related	1 (10)
Local injection-site reaction	1 (10)

- No serious AEs
- Only treatment-related AE was mild injection-site reaction
  - 2 events in 1 patient
- No thromboembolic or thrombotic microangiopathy events reported
- No patients tested positive for anti-drug antibodies

QW, weekly

HAVEN 2 Infants & Toddlers

Emicizumab Pharmacokinetics



- Trough plasma concentration of ~50 µg/mL achieved following first 4 weeks of treatment and maintained thereafter*
- Consistent with older paediatric patients in HAVEN 2 and adolescent/adult patients in HAVEN 1
  - No effect of age or body weight on plasma concentration over time

*Emicizumab administered at 3 mg/kg/wk for 4 weeks and 1.5 mg/kg/wk thereafter; data cutoff date for pharmacokinetic analysis was 1 August 2017.

CONCLUSIONES HAVEN 2

- Los resultados de Emicizumab en pacientes < 2 años son consistentes con los del estudio HAVEN1
- Eficacia en prevencion de sangrados
- Buen perfil de seguridad
  - No tromboembolismos . Eritema local 2 pacientes
- Farmacocinética igual que adolescentes y adultos

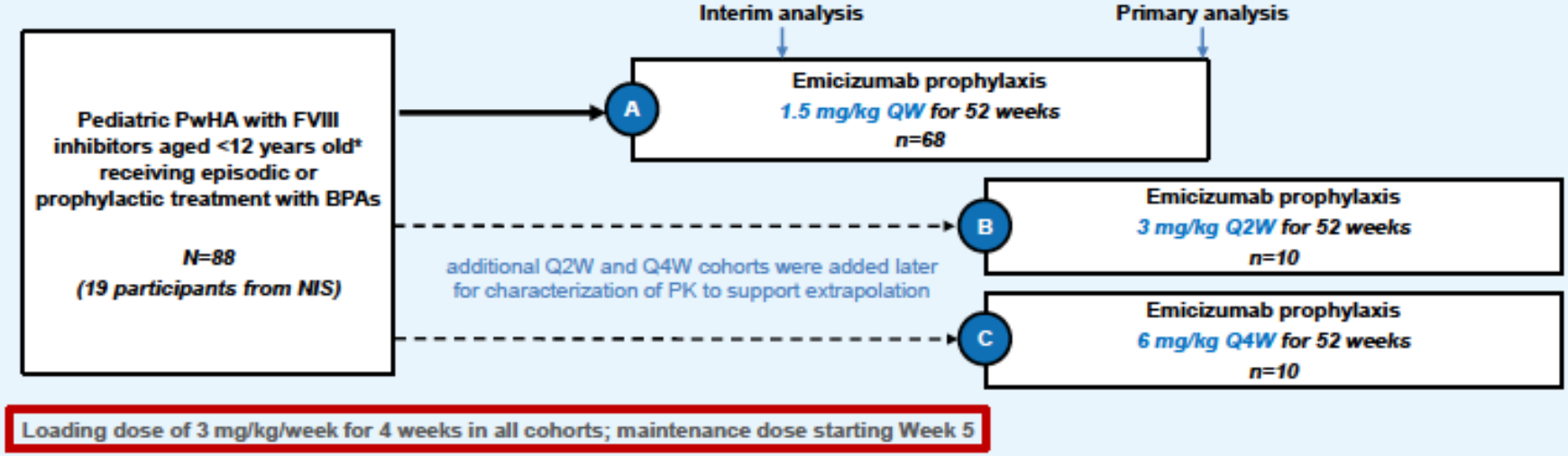
Emicizumab prophylaxis provides flexible and effective bleed control in children with hemophilia A with inhibitors: results from the HAVEN 2 study

Guy Young,[1] Ri Liesner,[2] Robert Sidonio Jr,[3] Johannes Oldenburg,[4] Victor Jimenez-Yuste,[5] Johnny Mahlangu,[6] Rebecca Kruse-Jarres,[7] Michael Wang,[8] Tiffany Chang,[9] Marianne Uguen,[10] Michelle Doral,[9] Christophe Schmitt,[10] Gallia Levy,[9] Midori Shima,[11] Maria Elisa Mancuso[12]

[1]Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA, USA;

HAVEN 2 study design

Multi-center, open-label, phase III study in pediatric participants with hemophilia A with FVIII inhibitors (NCT02795767)



Efficacy endpoints
- Bleeds over time†
- Intra-patient bleed rate comparison (for participants who were previously in the NIS)
- Quality of life

Safety endpoints
- Overall AEs
- AEs of interest: thrombotic events, ISR, severe hypersensitivity, anaphylaxis and anaphylactoid events, and ADAs

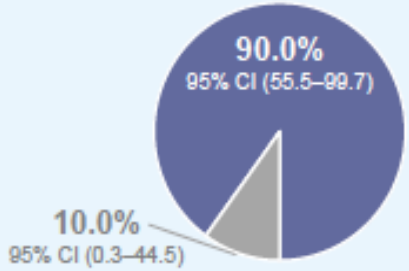
Pharmacokinetic endpoints
- Characterize emicizumab exposure to confirm the appropriate pediatric dose

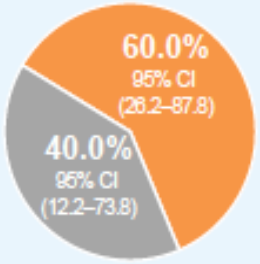
Primary analysis data cut-off: April 30, 2018

Clinically meaningful efficacy also seen with emicizumab Q2W and Q4W

Treated bleeds	3 mg/kg Q2W n=10	6 mg/kg Q4W n=10
ABR* (95% CI)	0.2 (0.03–1.72)	2.2 (0.69–6.81)
Median ABR, calculated (IQR)	0.0 (0.00–0.00)	0.0 (0.00–3.26)

Patients with zero treated bleeds
Patients with 1–3 treated bleeds

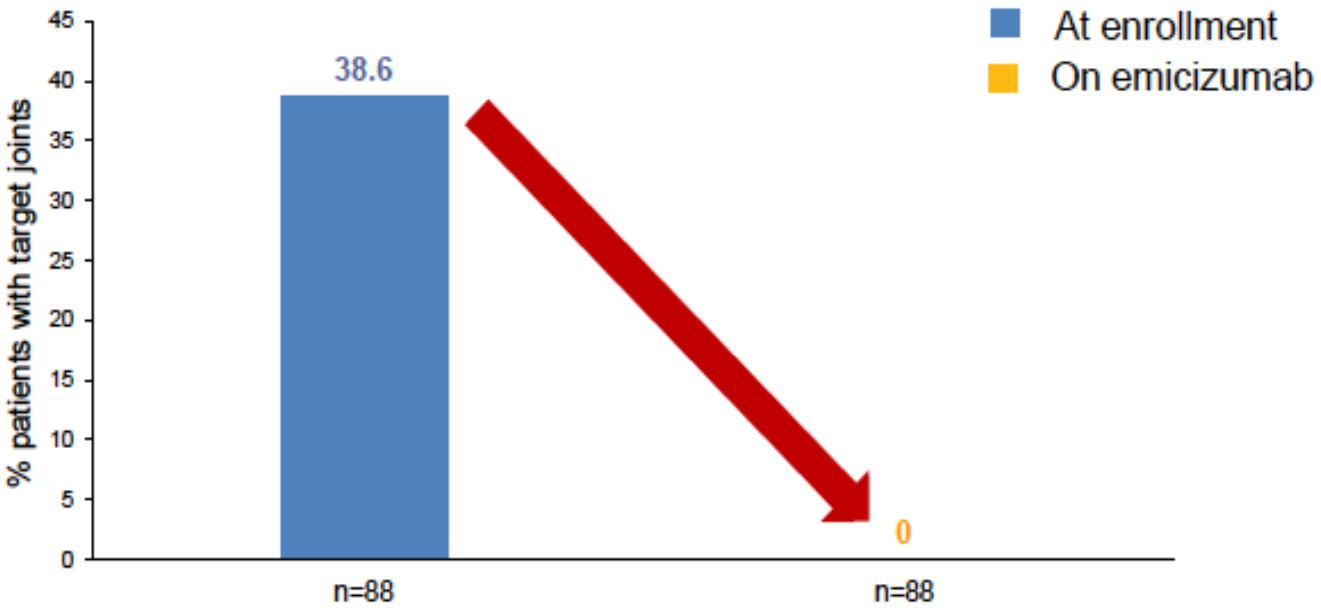




- Smaller population with shorter follow-up time:
  - Efficacy periods, median (range)
    - Q2W: 21.3 (18.6–24.1) weeks
    - Q4W: 19.9 (8.9–24.1) weeks
- **Across all three regimens, 100% of patients had ≤3 treated bleeds**

- Numerically higher ABR in Q4W cohort primarily driven by two patients
  - One with 6 target joint bleeds in the 24 weeks prior to enrolment experienced 3 joint bleeds over 20 weeks after study entry
  - Second developed ADA with neutralizing potential; experienced 2 bleeds within first 8 weeks on study

Proportion of patients with target joints* was reduced with emicizumab



- Incidence of target joints in a post-hoc analysis

Summary

- HAVEN 2 is the largest prospective bleed prevention study in pediatric PwHA with inhibitors
- In HAVEN 2, QW, Q2W, and Q4W treatment regimens provided clinically meaningful prevention or reduction of bleeds
  - Notably, an intraindividual comparison demonstrated 99% reduced risk of treated bleeds with emicizumab QW over prior episodic/prophylactic BPA treatment
- Emicizumab was well tolerated, with no TMA, thromboembolic events, or fatalities reported
- Therapeutic trough plasma concentrations were achieved and maintained with less frequent dosing
- Subcutaneous emicizumab prophylaxis may offer a highly efficacious and flexible treatment option, with reduced burden for children with hemophilia A

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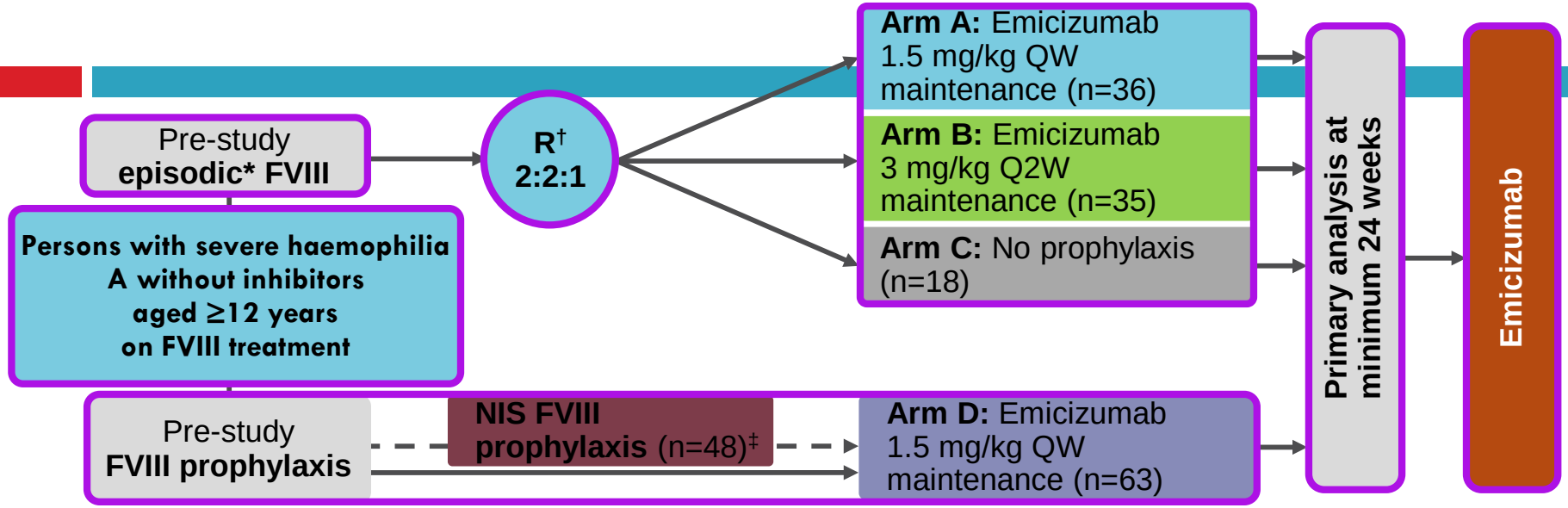
Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors

J. Mahlangu, J. Oldenburg, I. Paz-Priel, C. Negrier, M. Niggli, M.E. Mancuso, C. Schmitt, V. Jiménez-Yuste, C. Kempton, C. Dhalluin, M.U. Callaghan, W. Bujan, M. Shima, J.I. Adamkewicz, E. Asikanius, G.G. Levy, and R. Kruse-Jarres

CONCLUSIONS

Emicizumab prophylaxis administered subcutaneously once weekly or every 2 weeks led to a significantly lower bleeding rate than no prophylaxis among persons with hemophilia A without inhibitors; more than half the participants who received prophylaxis had no treated bleeding events. In an intraindividual comparison, emicizumab therapy led to a significantly lower bleeding rate than previous factor VIII prophylaxis. (Funded by F. Hoffmann–La Roche and Chugai Pharmaceutical; HAVEN 3 ClinicalTrials.gov number, NCT02847637.)



Emicizumab given subcutaneously and all regimens started with a loading series of 3 mg/kg/week for 4 weeks

Primary efficacy	Treated bleed rate (A vs C; B vs C) at minimum 24 weeks
Secondary efficacy	All bleed rate; joint bleed rate; target joint bleed rate; spontaneous bleed rate; HRQoL/health status Bleed rate in prophylaxis Arm D patients vs prior FVIII prophylaxis during NIS
Safety	Includes incidence of ADAs, TEs, FVIII inhibitors

NCT02847637: phase 3, open-label, multicentre, randomised study; initiated 27 Sept 27 2016; data cutoff 15 Sept 15 2017.
*Prior 24-week bleed rate ≥5 for patients receiving episodic FVIII.
†Randomisation stratified based on prior 24-week bleed rate of <9 or ≥9.

ADA, anti-drug antibody; HRQoL, health-related quality of life; QW, once weekly; Q2W, every 2 weeks; R, randomised; TE, thromboembolic event.

HAVEN 3 bleed-related secondary endpoints

Consistent statistically significant reductions in ABR across endpoints and regimens

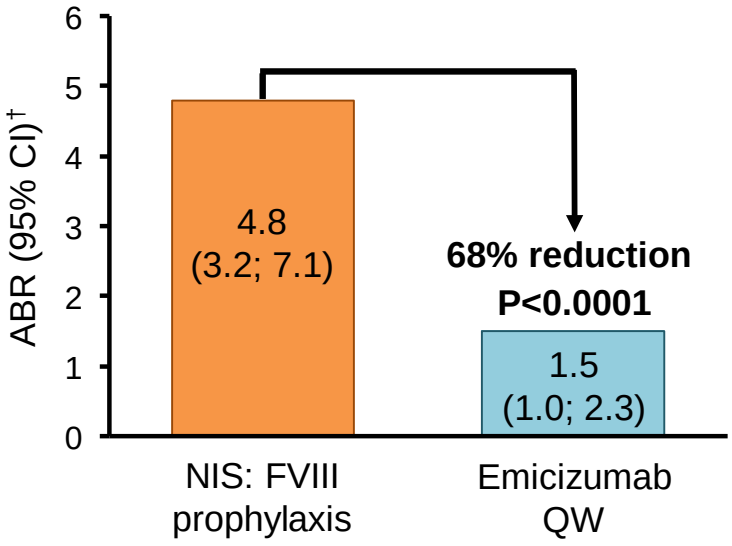
Endpoint	Arm A: Emicizumab 1.5 mg/kg QW n=36	Arm B: Emicizumab 3 mg/kg Q2W n=35	Arm C: No prophylaxis n=18
All bleeds			
ABR, model based* (95% CI)	2.5 (1.6; 3.9)	2.6 (1.6; 4.3)	47.6 (28.5; 79.6)
% reduction (RR) vs Arm C, P-value	**95%, P<0.0001**	**94%, P<0.0001**	—
% patients with 0 bleeds (95% CI)	50.0 (32.9; 67.1)	40.0 (23.9; 57.9)	0.0 (0.0; 18.5)
Treated spontaneous bleeds			
ABR, model based* (95% CI)	1.0 (0.5; 1.9)	0.3 (0.1; 0.8)	15.6 (7.6; 31.9)
% reduction (RR) vs Arm C, P-value	**94%, P<0.0001**	**98%, P<0.0001**	—
% patients with 0 bleeds (95% CI)	66.7 (49.0; 81.4)	88.6 (73.3; 96.8)	22.2 (6.4; 47.6)
Treated joint bleeds			
ABR, model based* (95% CI)	1.1 (0.6; 1.9)	0.9 (0.4; 1.7)	26.5 (14.7; 47.8)
% reduction (RR) vs Arm C, P-value	**96%, P<0.0001**	**97%, P<0.0001**	—
% patients with 0 bleeds (95% CI)	58.3 (40.8; 74.5)	74.3 (56.7; 87.5)	0.0 (0.0; 18.5)
Treated target joint bleeds			
ABR, model based* (95% CI)	0.6 (0.3; 1.4)	0.7 (0.3; 1.6)	13.0 (5.2; 32.3)
% reduction (RR) vs Arm C, P-value	**95%, P<0.0001**	**95%, P<0.0001**	—
% patients with 0 bleeds (95% CI)	69.4 (51.9; 83.7)	77.1 (59.9; 89.6)	27.8 (9.7; 53.5)

*ABR calculated with negative binomial regression model.

HAVEN 3: Intraindividual comparison of treated bleeds

Emicizumab significantly reduced ABR vs prior FVIII prophylaxis

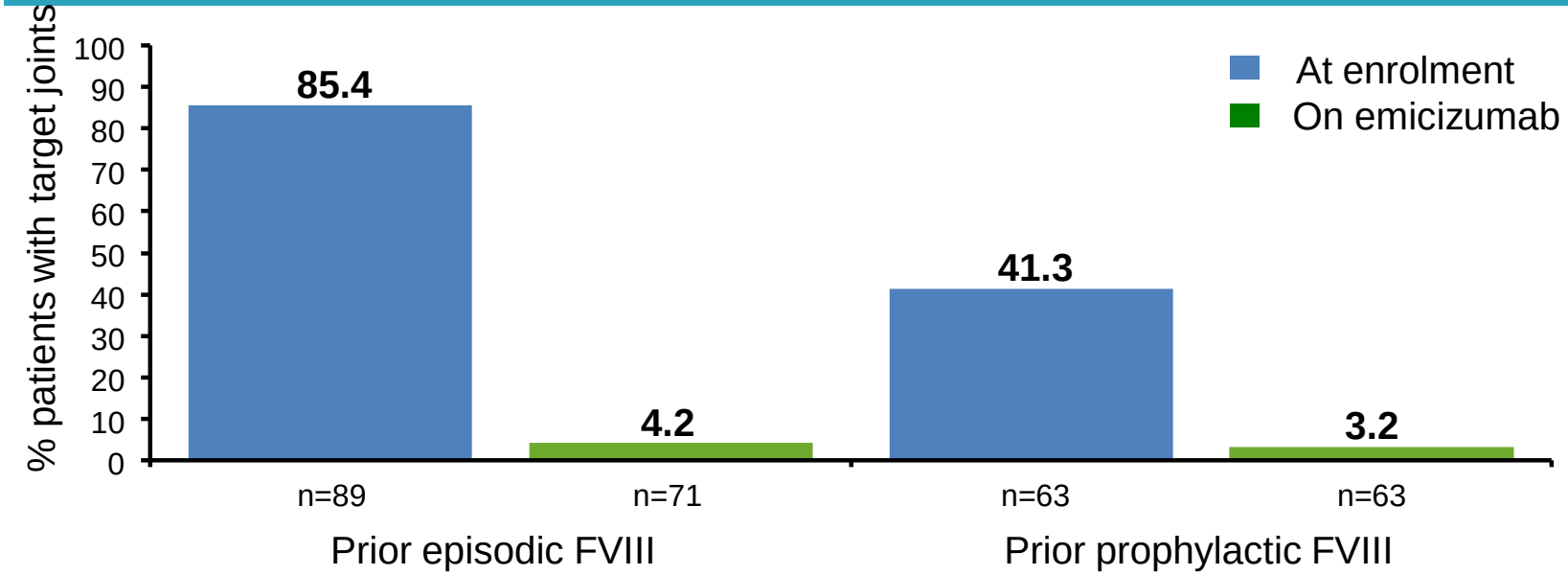
Endpoint	Arm D: Emicizumab 1.5 mg/kg QW n=48*	NIS: FVIII prophylaxis n=48
Duration of efficacy period, median (min-max), weeks	33.7 (20.1–48.6)	30.1 (5.0–45.1)
ABR, model based (95% CI)†	1.5 (1.0; 2.3)	4.8 (3.2; 7.1)
Reduction vs NIS FVIII RR, P-value	**68% reduction** 0.32, P<0.0001	—
Median ABR, calculated (IQR)	0.0 (0.0–2.1)	1.8 (0.0–7.6)
Patients with zero bleeds, % (95% CI)	54.2 (39.2; 68.6)	39.6 (25.8; 54.7)
Patients with 0–3 bleeds, % (95% CI)	91.7 (80.0; 97.7)	72.9 (58.2; 84.7)



- For all patients in Arm D (n=63), ABR (95% CI) was 1.6 (1.1; 2.4) and 55.6% (95% CI, 42.5; 68.1) had zero bleeds

*Data from 48 patients in Arm D who participated in the NIS shown.
†ABR calculated with negative binomial regression model.

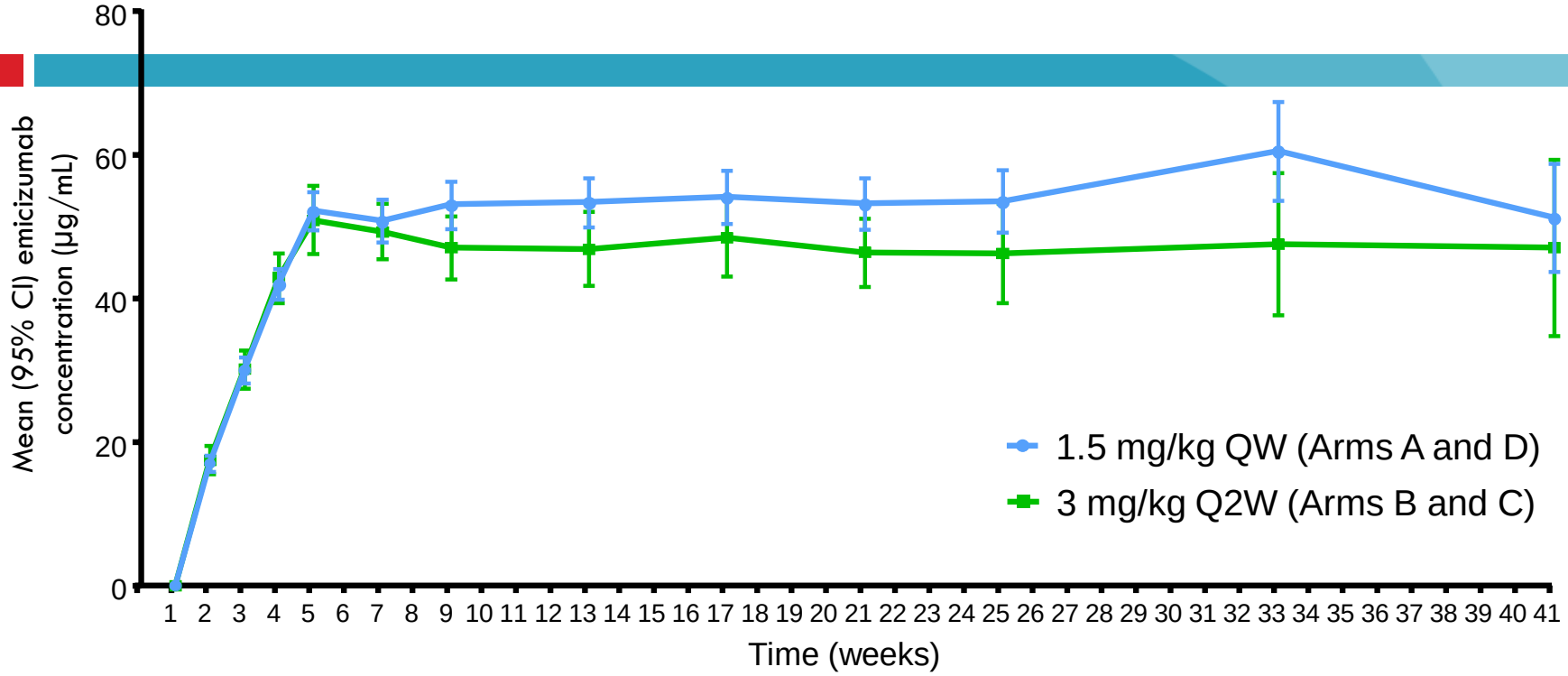
Proportion of patients with target joints



- Incidence of target joints in a post-hoc analysis

*Target joints are defined as a major joint into which ≥3 bleeds occur over a 24-week period. At study entry, the presence of target joints based on bleeds in the 24 weeks before enrolment was recorded. In a post-hoc analysis, target joints were identified within any 24-week period during emicizumab treatment (or the initial period for patients with <24 weeks of treatment) before up-titration (if applicable). Arm C patients after switchover to emicizumab were excluded from this analysis due to the limited follow-up period.

HAVEN 3: pharmacokinetics



- Emicizumab trough concentrations were consistent with a T ½ of ~30 days

Arm C data represents patients who switched to emicizumab prophylaxis after completing ≥24 weeks on study.
Yoneyama K, et al. *Clin Pharmacokinet* 2017 Epub.

CONCLUSIONES HAVEN 3

- Emicizumab en profilaxis muestra unos resultados de alta eficacia en pacientes sin inhibores , tanto en pauta semanal como quincenal
- Mejora notablemente los resultados de la profilaxis con Factor VIII:C
- Buen perfil de seguridad : No TEV , No MAT

Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study

Steven W Pipe, Midori Shima, Michaela Lehle, Amy Shapiro, Sammy Chebon, Katsuyuki Fukutake, Nigel S Key, Agnès Portron, Christophe Schmitt, Maria Podolak-Dawidziak, Nives Selak Bienz, Cedric Hermans, Avrita Campinha-Bacote, Anna Kiialainen, Kathelijne Peerlinck, Gallia G Levy, Victor Jiménez-Yuste

Interpretation Emicizumab given once every 4 weeks showed clinically meaningful bleed control while being well tolerated. This regimen could improve patient care by decreasing treatment burden and increasing adherence to effective prophylaxis, potentially decreasing the development of secondary complications for people with haemophilia A.

Pipe SW et al Lancet Hematol 2019

PK run-in cohort (n=7)
PwHA aged ≥12 years (prior episodic treatment); emicizumab 6 mg/kg Q4W* for ≥24 weeks

Analyses
PK and safety (last patient at Week 6 of treatment)

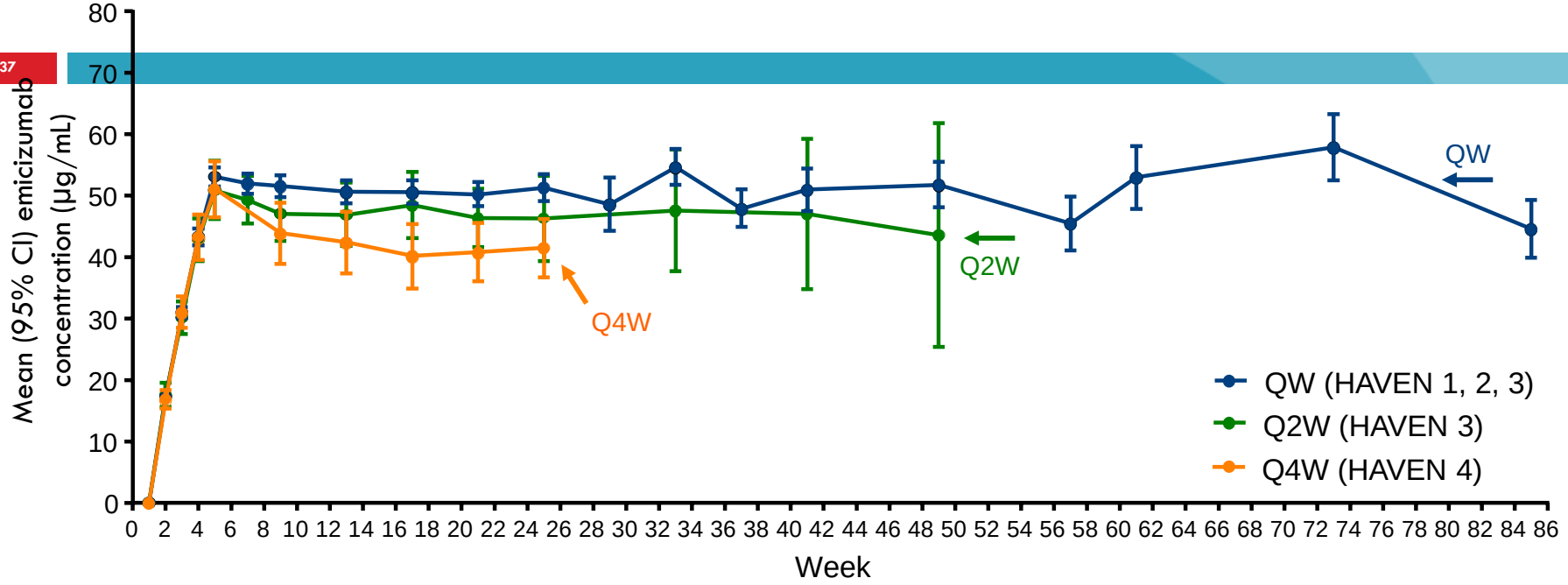
Expansion cohort (n=41)
Loading dose:
Emicizumab 3 mg/kg QW for 4 weeks, followed by
Maintenance dose:
Emicizumab 6 mg/kg Q4W for ≥24 weeks

Analyses
Efficacy, safety, PK/PD

- Expansion cohort:
  - Severe haemophilia A with or without inhibitors
  - Documented episodic or prophylactic treatment with FVIII replacement or BPAs for ≥24 weeks before study entry
  - Median (range) efficacy period: 25.6 (24.1–29.4) weeks

NCT03020160: phase 3, open-label, multicentre, randomised study. Data cutoff: 15 December 2017.
*Dosing regimens different in PK run-in and expansion cohorts.

PD, pharmacodynamics; Q4W, every 4 weeks.



- Clinically efficacious concentrations obtained with all 3 dosing regimens (consistent with PK model predictions)
- For Q4W, emicizumab mean trough concentrations were maintained at ~41 µg/mL from Week 13 to Week 25

Yoneyama K, et al. *Clin Pharmacokinet* 2017 Epub.

HAVEN 4: Effectivity with emicizumab Q4W

Bleeds n=41 pts	ABR, model based (95% CI)*	Median ABR, calculated (IQR)	Zero bleeds, % pts (95% CI)	0–3 bleeds, % pts (95% CI)
Treated bleeds	2.4 (1.4; 4.3)	0.0 (0.0; 2.1)	56.1 (39.7; 71.5)	90.2 (76.9; 97.3)
All bleeds	4.5 (3.1; 6.6)	2.1 (0.0; 5.9)	29.3 (16.1; 45.5)	80.5 (65.1; 91.2)
Treated spontaneous bleeds	0.6 (0.3; 1.5)	0.0 (0.0; 0.0)	82.9 (67.9; 92.8)	97.6 (87.1; 99.9)
Treated joint bleeds	1.7 (0.8; 3.7)	0.0 (0.0; 1.9)	70.7 (54.5; 83.9)	95.1 (83.5; 99.4)
Treated target joint bleeds	1.0 (0.3; 3.3)	0.0 (0.0; 0.0)	85.4 (70.8; 94.4)	97.6 (87.1; 99.9)

Data cutoff: 15 Dec 2017.
*ABR calculated with negative binomial regression model.

IQR, interquartile range; pt, patient.

HAVEN 4 : Safety profile

	Emicizumab 6 mg/kg Q4W N=41
Total number of AEs	148
Total patients ≥1 AE, n (%)	30 (73.2)
Serious AE*	1 (2.4)
Grade ≥3 AE	1 (2.4)
Related AE	12 (29.3)
Local injection-site reaction	9 (22.0)
AEs of special interest, n (%)	
Hypersensitivity	0
TE/TMA	0

73.2% of patients experienced ≥1 AE

- Only 1 serious (Grade ≥3) AE of rhabdomyolysis unrelated to emicizumab
- Injection-site reaction was the most common emicizumab-related AE (22.0%)
- No AEs led to emicizumab discontinuation or withdrawal
- No TEs, TMAs or hypersensitivity reactions
- No ADAs detected; no patients developed *de novo* FVIII inhibitors

Data cutoff: 15 Dec 2017.
*1 serious AE in the PK run-in cohort: grade 3 hypertension in patient with medical history of hypertension; unrelated to emicizumab treatment.

TE, thromboembolism; TMA, thrombotic microangiopathy.

CONCLUSIONES HAVEN 4

- Emicizumab cada 4 semanas fue seguro y eficaz en pacientes > 12 años con o sin inhibidores
- Los resultados en eficacia y seuridad fueron consistentes con el resto de estudios HAVEN
- El perfil farmacocinético se asocia ala respuesta clinica .

Effects and Interferences of Emicizumab, a Humanised Bispecific Antibody Mimicking Activated Factor VIII Cofactor Function, on Coagulation Assays

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Thromb Haemost

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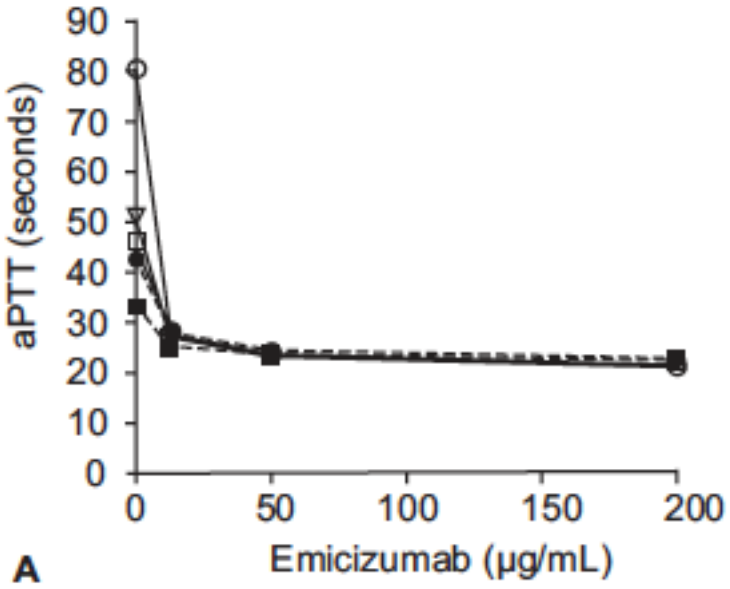
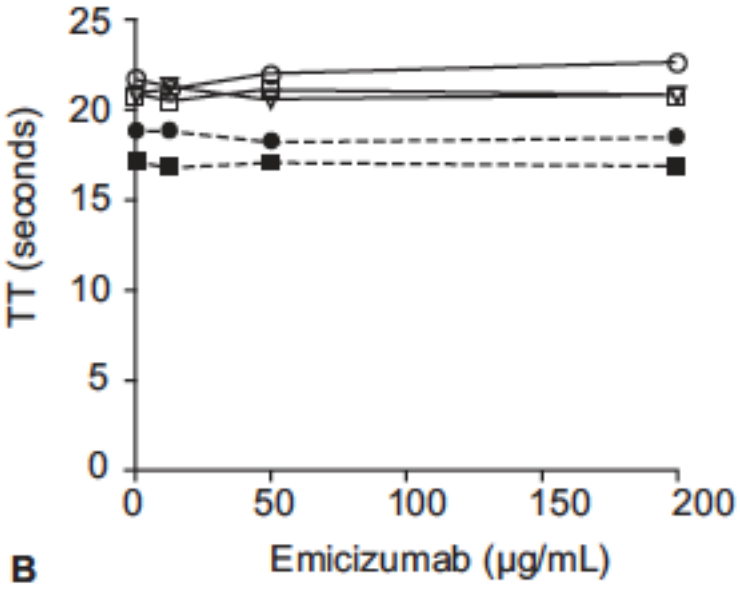
Pruebas de Hemostasia NO afectadas

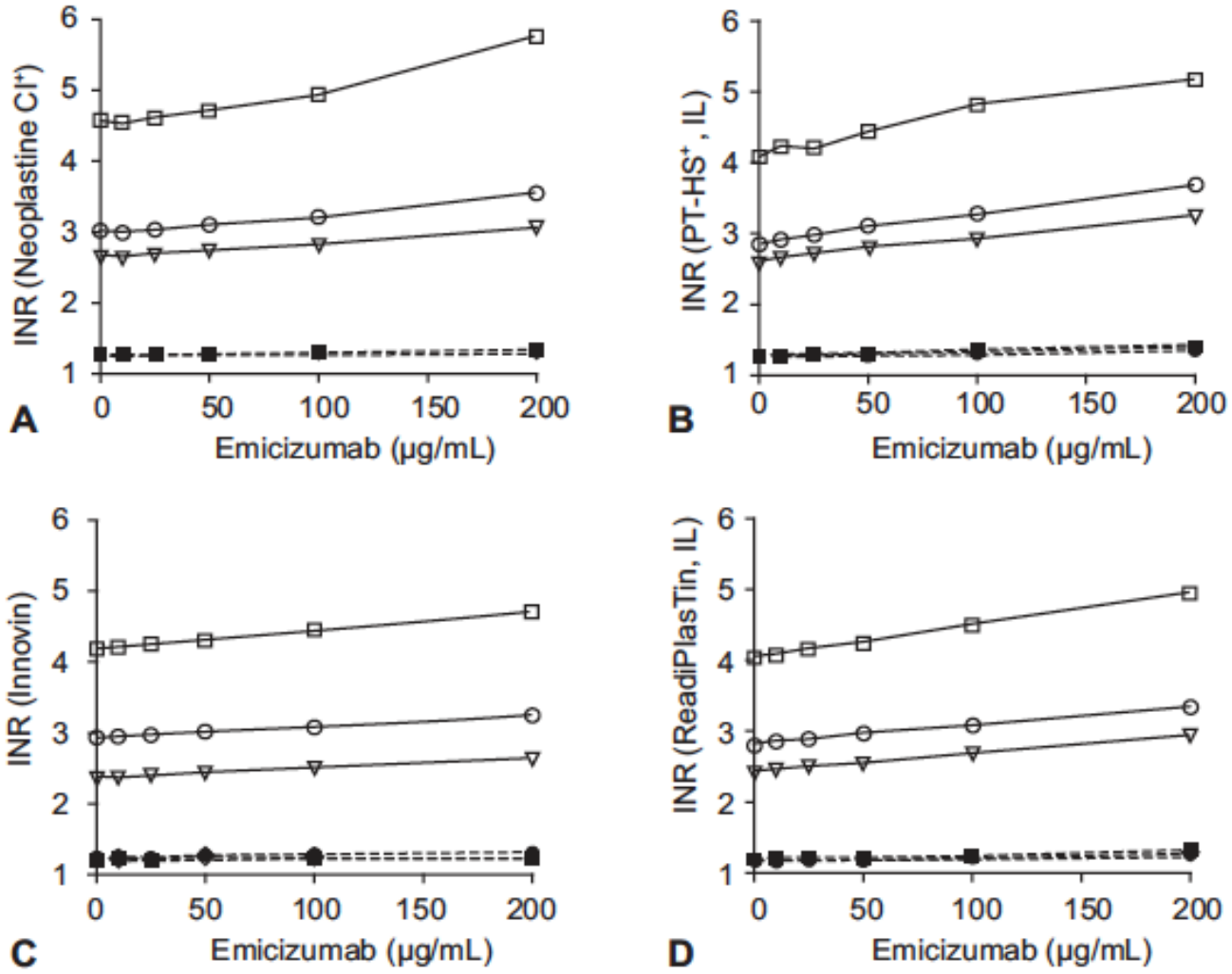
Assay	Principle	Activator
Fibrinogen according to Clauss	Clotting assay	Thrombin
Thrombin time		
Prothrombin activator-based APC resistance test		Prothrombin activator
Anti-Xa activity	Amidolytic assay	FXa
Protein C chromogenic assay		Protein C activator
Antithrombin activity		Thrombin
Plasminogen activity		Streptokinase
Plasminogen antigen	ELISA	Not applicable
Free protein S antigen	Latex assay	
D-dimer concentration		
vWF antigen		
vWF activity		
FXIII antigen		

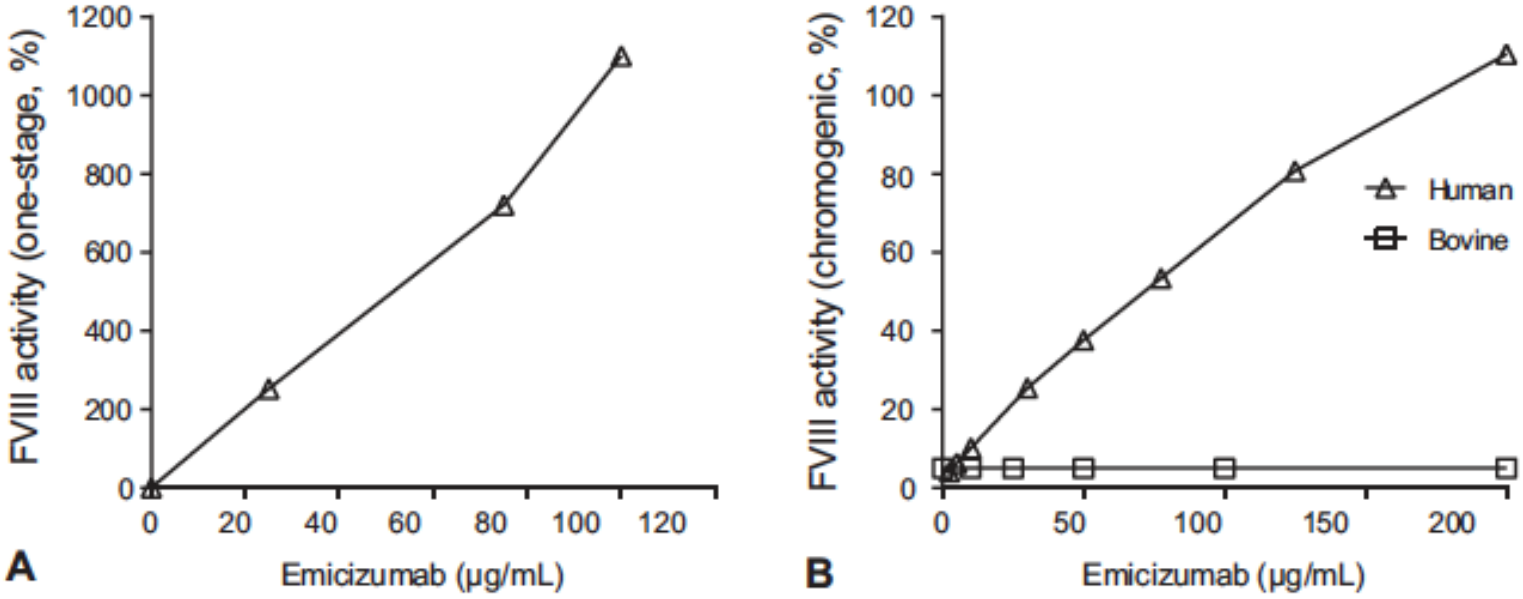
Pruebas de Hemostasia SI afectadas

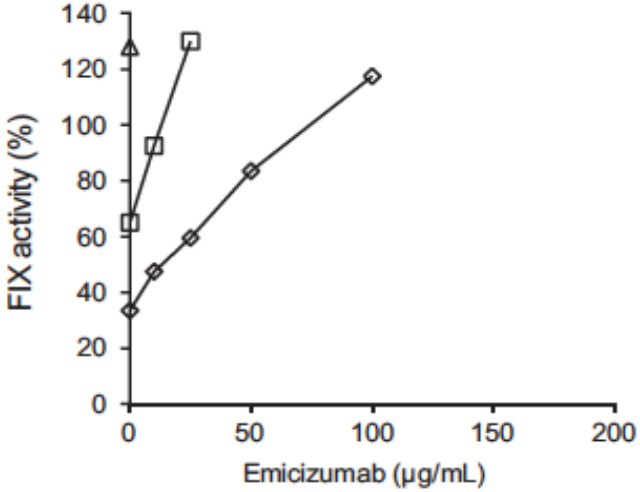
Assay	Principle	Activator	Mitigation
aPTT	Clotting (chronometric)	Contact activator (kaolin, silica, etc.)	For heparin monitoring: anti-Xa assay
aPTT-based protein C assay		Protein C activator	Chromogenic protein C assay
aPTT-based protein S assay		Contact activator/ APC/FVa	Free protein S assay
aPTT-based APC resistance assay		Contact activator/ APC	Prothrombin activator-based test for APC resistance, gene test for FV Leiden mutation
PT (weak effect)		TF	No mitigation required (small effect); PT reagent selection also will mitigate
Derived fibrinogen (weak effect)	Clotting (photometric)		No mitigation required (small effect); also Clauss fibrinogen is unaffected by emicizumab

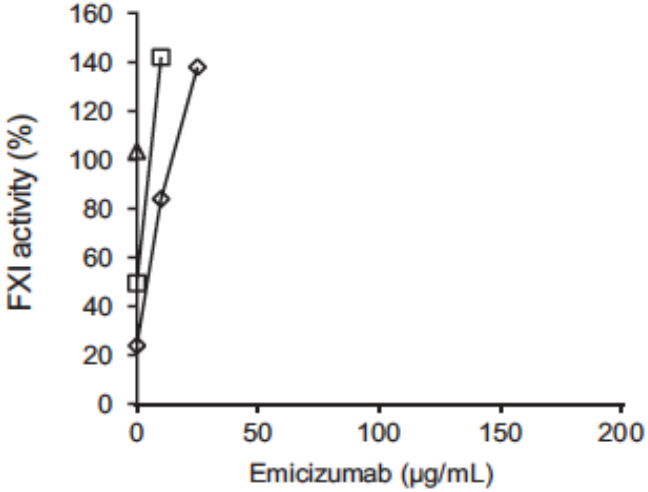

90
80
70
60
50
40
30
20
10
0
aPTT (seconds)
0
50
100
150
200
Emicizumab (µg/mL)
A

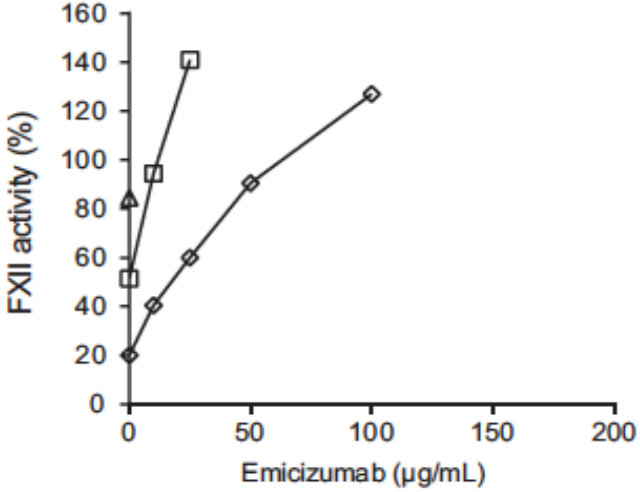

25
20
15
10
5
0
TT (seconds)
0
50
100
150
200
Emicizumab (µg/mL)
B

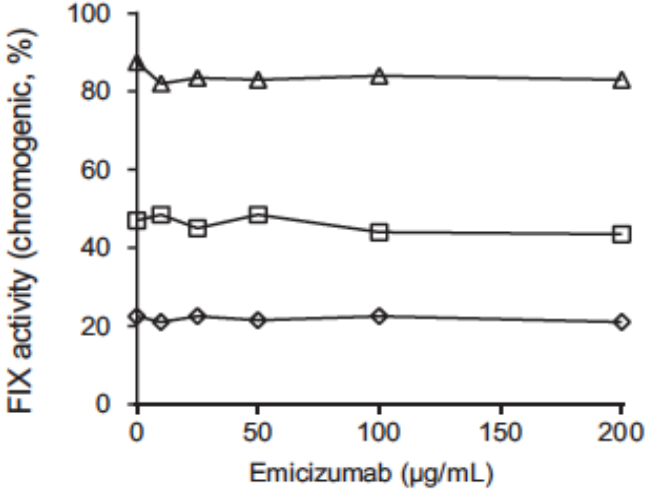

A
INR (Neoplastine CI+)
Emicizumab (µg/mL)
B
INR (PT-HS+, IL)
Emicizumab (µg/mL)
C
INR (Innovin)
Emicizumab (µg/mL)
D
INR (ReadiPlasTin, IL)
Emicizumab (µg/mL)


FVIII activity (one-stage, %)
1200
1000
800
600
400
200
0
0
20
40
60
80
100
120
A
Emicizumab (µg/mL)
FVIII activity (chromogenic, %)
120
100
80
60
40
20
0
0
50
100
150
200
Human
Bovine
B
Emicizumab (µg/mL)


FIX activity (%)
140
120
100
80
60
40
20
0
0
50
100
150
200
Emicizumab (µg/mL)


FXI activity (%)
160
140
120
100
80
60
40
20
0
0
50
100
150
200
Emicizumab (µg/mL)


FXII activity (%)
160
140
120
100
80
60
40
20
0
0
50
100
150
200
Emicizumab (µg/mL)


FIX activity (chromogenic, %)
100
80
60
40
20
0
0
50
100
150
200
Emicizumab (µg/mL)

Results affected by EMICIZUMAB	Results unaffected by EMICIZUMAB
• Activated partial thromboplastin time (aPTT) • Bethesda assays (clotting-based) for FVIII inhibitor titres • One-stage, aPTT-based, single-factor assays • aPTT-based activated protein C resistance (APC-R) • Activated clotting time (ACT)	• Bethesda assays (bovine chromogenic) for FVIII inhibitor titres • Thrombin time (TT) • One-stage, prothrombin time (PT)-based, single-factor assays • Chromogenic-based single-factor assays other than FVIII • Immuno-based assays (e.g. ELISA, turbidimetric methods) • Genetic tests of coagulation factors (e.g. Factor V Leiden, Prothrombin 20210)