Supplementary appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Rurioctocog alfa pegol PK-guided prophylaxis in hemophilia A: Results from the phase 3 PROPEL study

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Trial registration

The PROPEL study (NCT02585960) was first submitted to ClinicalTrials.gov on October 21, 2015. The first patient's first visit was on November 23, 2015.

Supplemental methods

Inclusion criteria

Patients transitioning from another rurioctocog alfa pegol study who met all of the following criteria were eligible for this study: completed the end of study visit of a rurioctocog alfa pegol study (NCT01599819,[1] NCT01736475,[1] NCT02210091,[2] NCT02615691, NCT01913405,[3] or NCT01945593[4]); receiving on-demand or prophylactic treatment with rurioctocog alfa pegol with an annualized bleeding rate (ABR) ≥ 2 during the 12 months before study entry; negative for human immunodeficiency virus (HIV-), or HIV+ with stable disease and a CD4+ count ≥200 cells/mm^3 as confirmed by central laboratory; willing and able to comply with the requirements of the protocol.

Newly recruited patients, including those naïve to rurioctocog alfa pegol, who met all of the following criteria were eligible for this study: 12-65 years of age at the time of screening; diagnosis of severe hemophilia A (factor VIII [FVIII] clotting activity <1%) as confirmed by a central laboratory, or by historically documented FVIII clotting activity performed by a certified clinical laboratory and/or a FVIII gene mutation consistent with severe hemophilia A; previously treated with plasma-derived FVIII concentrates or recombinant FVIII for ≥150 documented exposure days (EDs); receiving on-demand or prophylactic treatment with an ABR ≥ 2 during the 12 months before study entry; Karnofsky performance score of ≥60 at screening; diagnosis of HIV-, or HIV+ with stable disease and a CD4+ count ≥200 cells/mm^3 as confirmed by central laboratory at screening; negative for hepatitis C virus (HCV-) by antibody (if positive, additional polymerase chain reaction [PCR] testing will be performed), as confirmed by central laboratory at screening, or HCV+ with chronic stable hepatitis; if female and of childbearing potential, patient presents with a negative urine pregnancy test

and agrees to employ adequate birth control measures for the duration of the study; willing and able to comply with the requirements of the protocol.

Exclusion criteria

Patients transitioning from another rurioctocog alfa pegol study who met any of the following criteria were not eligible for this study: developed a confirmed inhibitory antibody to FVIII with a titer of ≥0.6 Bethesda units (BU) using the Nijmegen modification of the Bethesda assay as determined at the central laboratory during the course of the previous rurioctocog alfa pegol study; diagnosed with an acquired hemostatic defect other than hemophilia A; body weight <35 kg or >100 kg; platelet count <100 000/mL; abnormal renal function (serum creatinine >1.5 times the upper limit of normal); active hepatic disease with alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels ≥5 times the upper limit of normal; scheduled to receive a systemic immunomodulating drug (eg, corticosteroid agents at a dose equivalent to hydrocortisone >10 mg/day, or α-interferon) other than antiretroviral chemotherapy during the study; any clinically significant medical, psychiatric, or cognitive illness or recreational drug/alcohol use that, in the opinion of the investigator, would affect the patient's safety or compliance; patient is planning to take part in any other clinical study during the course of the study; patient is a member of the team conducting this study or is in a dependent relationship with one of the study team members. Dependent relationships include close relatives (ie, child, partner/spouse, sibling, parent) as well as employees of the investigator or site personnel conducting the study.

Newly recruited patients who met any of the following criteria were not eligible for this study: has detectable FVIII inhibitory antibodies (≥0.6 BU using the Nijmegen modification of the Bethesda assay) as confirmed by a central laboratory at screening; history of confirmed FVIII inhibitors with a titer ≥0.6 BU (as determined by the Nijmegen modification of the Bethesda assay or the assay employed with the respective cutoff in the local laboratory) at any time prior to screening; diagnosis of an inherited or acquired hemostatic defect other than

hemophilia A (eg, qualitative platelet defect or von Willebrand's disease); body weight <35 kg or >100 kg; platelet count <100 000/mL; hypersensitivity towards mouse or hamster proteins, polyethylene glycol (PEG), or Tween 80; severe chronic hepatic dysfunction [eg, ≥5 times upper limit of normal ALT and/or AST, as confirmed by a central laboratory at screening, or a documented international normalized ratio [INR] >1.5]; severe renal impairment (serum creatinine >1.5 times the upper limit of normal); current or recent (<30 days) use of other pegylated drugs prior to study participation or patient scheduled to use such drugs during study participation; patient scheduled to receive, during the course of the study, a systemic immunomodulating drug (eg, corticosteroid agents at a dose equivalent to hydrocortisone >10 mg/day, or α-interferon) other than antiretroviral chemotherapy; patient has participated in another clinical study involving an investigational product or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an investigational product or device during the course of this study; medical, psychiatric, or cognitive illness or recreational drug/alcohol use that, in the opinion of the investigator, would affect the patient's safety or compliance; patient is a member of the team conducting this study or is in a dependent relationship with one of the study team members. Dependent relationships include close relatives (ie, child, partner/spouse, sibling, parent) as well as employees of the investigator or site personnel conducting the study.

Study treatment guidelines for breakthrough bleeding events

In case of a breakthrough bleeding, rurioctocog alfa pegol (10-60 ± 5 IU/kg) was used according to preestablished treatment guidelines (dose and frequency for minor, moderate, and major bleeds), with individual incremental recovery (IR) taken into consideration when possible. Patients with hemophilia A resumed their pharmacokinetic (PK)-tailored prophylaxis following resolution of the bleeding episode. Treatment guidelines are as follows:

Minor bleeds include early hemarthrosis, mild muscle bleeding, or mild oral bleeding, including epistaxis. For these bleeds, a FVIII level of 20-40% is required, using a rurioctocog alfa pegol dose of 10-20 (± 5) IU/kg. Repeat infusions every 12-24 hours for 1-3 days or until the bleeding episode is resolved.

Moderate bleeds include moderate bleeding into muscles, bleeding into the oral cavity, definite hemarthrosis, and known trauma. For these bleeds, a FVIII level of 30-60% is required, using a rurioctocog alfa pegol dose of 15-30 (± 5) IU/kg. Repeat infusions every 12-24 hours for ≥3 days or until the pain and acute disability/incapacity are resolved.

Major bleeds include significant gastrointestinal bleeding; intracranial, intra-abdominal, or intrathoracic bleeding; central nervous system bleeding; bleeding in the retropharyngeal or retroperitoneal spaces or iliopsoas sheath; fractures; and head trauma. For these bleeds, a FVIII level of 60-100% is required, using a rurioctocog alfa pegol dose of 30-60 (±5) IU/kg. In the case of life-threatening bleeds, a dose of 80 (±5) IU/kg may be considered. Repeat infusions every 8-12 hours until the bleeding episode/threat is resolved.

Study treatment guidelines for planned surgery or dental procedures

Patients who required planned surgery or dental procedures were treated according to the treatment recommendation including a FVIII substitution plan. Patients who underwent surgical procedures resumed their PK-tailored dosing regimen following intensified peri-surgical treatment.

Definition of bleeding event

A bleeding event was defined either as subjective, characterized by pain consistent with a joint bleed, for example, or as objective, with evidence of a bleed. Bleeds of the same type that occurred at the same anatomical location within 72 hours of onset of the first bleed were considered a single bleed.[5] A new bleed was defined as occurring >72 hours after stopping a treatment for which the initial response was moderate to excellent.[5] Bleeding that occurred

at multiple locations but was related to the same injury was counted as a single bleeding episode.

FVIII activity assay

One-stage clotting assays were run on BCS/XP automated instruments (Siemens, Munich, Germany) with the activator reagent Actin FSL (Siemens, Munich, Germany). Chromogenic assays were run on BCS/XP automated instruments (Siemens, Munich, Germany) with the Chromogenix SP/4 FVIII kit (DiaPharma Group, West Chester Township, Ohio, USA). Only the one-stage clotting assay results are reported.

Supplemental tables

Supplemental Table 1. Frequency of planned rurioctocog alfa pegol dosing intervals used by study end (FAS)

	FAS, N = 115	
	FVIII trough level 1-3%, n = 57	**FVIII trough level 8-12%, n = 58**
PwHA per planned dosing interval,* n (%)		
24 h	0	7 (12.1)
36 h	0	8 (13.8)
48 h	11 (19.3)	35 (60.3)
72 h	11 (19.3)	7 (12.1)
72 or 96 h (alternating)†	4 (7.0)	0
84 h	23 (40.4)	0
96 h	8 (14.0)	1 (1.7)

FAS, full analysis set; FVIII, factor VIII; PK, pharmacokinetic; PwHA, people with hemophilia A.

*The dosing interval was determined at the beginning of the study after the initial PK assessment, and patients were instructed to adhere to the planned infusion interval as closely as possible.

†PwHA on an alternating 3- and 4-day infusion interval schedule administered the corresponding 3-day or 4-day interval dose.

Supplemental Table 2. Change in physical activity from baseline to study completion (FAS)

	FAS (N=115)	
	FVII trough level 1-3%, n = 57	**FVIII trough level 8-12%, n = 58**
Number of days with >15 minutes of activity per week, mean (SD)		
Mild activity	0.2 (2.9)	0.0 (2.7)
Moderate activity	1.1 (2.2)	0.6 (2.7)
Strenuous activity	0.3 (2.2)	0.4 (2.1)

FAS, full analysis set; FVIII, factor VIII; SD, standard deviation.

Supplemental Table 3. Total ABR (12-month study period) compared with ABR in the 12 months before study enrollment (FAS and PPAS)

	FAS, N = 115		PPAS, N = 95	
	FVII trough level 1-3%, n = 57	**FVIII trough level 8-12%, n = 58**	**FVIII trough level 1-3%, n = 52**	**FVIII trough level 8-12%, n = 43**
Total ABR during 12 months before enrollment				
Mean (SD)	13.3 (15.9)	13.3 (17.4)	11.8 (14.0)	14.3 (18.5)
Median (Q1-Q3)	6.0 (3.0-14.0)	5.0 (2.0-16.0)	6.0 (3.0-13.0)	7.0 (2.0-20.0)
Total ABR during extended observation period				
Mean (SD)	3.3 (6.4)	2.2 (3.5)	2.6 (2.7)	1.7 (3.0)
Median (Q1-Q3)	2.0 (1.0-4.0)	1.0 (0.0-4.0)	2.0 (0.5-3.5)	1.0 (0.0-2.0)
Intraindividual ratio of total ABR observed in PROPEL vs before enrollment*				
Mean (SD)	0.5 (0.7)	0.4 (0.7)	0.5 (0.7)	0.2 (0.4)
Median (Q1-Q3)	0.3 (0.0-0.8)	0.0 (0.0-0.5)	0.2 (0.0-0.8)	0.0 (0.0-0.3)

ABR, annualized bleeding rate; FAS, full analysis set; FVIII, factor VIII; PPAS, per-protocol analysis set; Q, quartile; SD, standard deviation.

*Data are reported as the mean and median of all the intraindividual ratios.

Supplemental Table 4. ABRs (second 6-month study period; FAS and PPAS): additional secondary efficacy outcomes

	FAS, N = 115		PPAS, N = 95	
	FVIII trough level 1-3%, n = 57	FVIII trough level 8-12%, n = 53*	FVIII trough level 1-3%, n = 52	FVIII trough level 8-12%, n = 43
Non-joint ABR				
Mean (SD)	1.0 (1.8)	0.6 (1.6)	1.0 (1.8)	0.4 (0.9)
Median (Q1-Q3)	0.0 (0.0-2.0)	0.0 (0.0-0.0)	0.0 (0.0-2.0)	0.0 (0.0-0.0)
Major ABR				
Mean (SD)	0.5 (2.9)	0.0 (0.3)	0.1 (0.6)	0.0 (0.3)
Median (Q1-Q3)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Moderate ABR				
Mean (SD)	2.0 (4.5)	0.9 (2.0)	1.5 (1.9)	0.7 (1.7)
Median (Q1-Q3)	0.0 (0.0-2.0)	0.0 (0.0-2.0)	0.0 (0.0-3.0)	0.0 (0.0-2.0)
Minor ABR				
Mean (SD)	1.1 (1.9)	0.7 (2.7)	1.2 (1.9)	0.5 (1.7)
Median (Q1-Q3)	0.0 (0.0-2.0)	0.0 (0.0-0.0)	0.0 (0.0-2.0)	0.0 (0.0-0.0)

ABR, annualized bleeding rate; FAS, full analysis set; FVIII, factor VIII; PPAS, per-protocol analysis set; PwHA, people with hemophilia A; Q, quartile; SD, standard deviation.

*ABR based on 53 PwHA; data not available from 5 randomized PwHA who discontinued the study prior to the second 6-month period.

Supplemental Table 5. Remaining joints with ≥4 spontaneous bleeds at 6 months (182 days) and 12 months (364 days) of rurioctocog alfa pegol prophylaxis (FAS)

	FVIII trough level 1-3%		FVIII trough level 8-12%		All PwHA	
	Day 182	**Day 364**	**Day 182**	**Day 364**	**Day 182**	**Day 364**
PwHA, n*	57	53	53	51	110	104
Remaining joints with ≥4 spontaneous bleeds, n (PwHA, n)						
Ankle	1 (1)	1 (1)	0 (0)	0 (0)	1 (1)	1 (1)
Knee	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)
Hip	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Elbow	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Total	2 (1)	1 (1)	1 (1)	0 (0)	3 (2)	1 (1)

FAS, full analysis set; FVIII, factor VIII; PwHA, people with hemophilia A.

Day number represents days since first prophylactic dose after randomization.

*The change in the number of joints with ≥4 spontaneous bleeds from baseline was assessed in 110 of 115 PwHA who had ≥6 months of observation during the 12-month study period.

Supplemental Table 6. ABR (second 6-month study period; PPAS) stratified by prior treatment regimen

	PPAS, N = 95			
	On-demand treatment before enrollment		Prophylactic treatment before enrollment	
	FVIII trough level 1-3%, n = 13	FVIII trough level 8-12%, n = 13	FVIII trough level 1-3%, n = 39	FVIII trough level 8-12%, n = 30
Total ABR				
Point estimate (95% CI) of mean	1.8 (1.0-3.3)	0.3 (0.1-1.2)	2.9 (2.0-4.3)	1.5 (0.9-2.6)
Point estimate (95% CI) of mean, ratio of 1-3% vs 8-12% FVIII trough levels	5.5 (1.2-25.7)		1.7 (0.9-3.3)	
Spontaneous ABR				
Point estimate (95% CI) of mean	0.8 (0.3-1.9)	0.1 (0.0-1.0)	1.9 (1.2-3.2)	0.7 (0.3-1.5)
Point estimate (95% CI) of mean, ratio of 1-3% vs 8-12% FVIII trough levels	3.9 (0.4-35.7)		2.7 (1.1-6.7)	
Spontaneous joint ABR				
Point estimate (95% CI) mean	0.8 (0.3-2.0)*	0.0 (NC)*	1.3 (0.7-2.4)	0.5 (0.2-1.3)
Point estimate (95% CI) of mean, ratio of 1-3% vs 8-12% FVIII trough levels	NC		2.6 (0.9-8.0)	
Injury-related ABR				
Point estimate (95% CI) of mean	0.9 (0.3-2.4)	0.2 (0.0-1.2)	0.8 (0.5-1.6)	0.8 (0.4-1.6)
Point estimate (95% CI) of mean, ratio of 1-3% vs 8-12% FVIII trough levels	6.5 (0.7-62.2)		0.9 (0.3-2.3)	

ABR, annualized bleeding rate; CI, confidence interval; FVIII, factor VIII; NC, not calculable; PPAS, per-protocol analysis set.

*Negative binomial distribution was substituted with Poisson distribution in the model to improve stability.

Supplemental Table 7. Rurioctocog alfa pegol treatment of breakthrough bleeding events (12-month study period; FAS and PPAS)

	FAS		PPAS	
	FVIII trough level 1-3%	**FVIII trough level 8-12%**	**FVIII trough level 1-3%**	**FVIII trough level 8-12%**
Total number of treated bleeds	155	87	112	49
Total number of infusions to treat a bleed	245	141	167	60
Number of infusions to treat a bleed				
Mean (SD)	1.6 (1.1)	1.6 (1.3)	1.5 (1.2)	1.2 (0.5)
Median (Q1-Q3)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-1.5)	1.0 (1.0-1.0)
Range	1.0-9.0	1.0-8.0	1.0-9.0	1.0-3.0
Dose per infusion to treat a bleed, IU/kg				
Mean (SD)	32.2 (12.8)	39.6 (14.5)	30.6 (13.6)	35.5 (14.5)
Median (Q1-Q3)	32.4 (20.8-37.9)	35.0 (32.0-53.0)	27.3 (20.0-38.1)	33.4 (25.4-45.0)
Range	8.0-68.3	14.9-76.5	8.0-68.3	15.0-76.5

FAS, full analysis set; FVIII, factor VIII; PPAS, per-protocol analysis set; Q, quartile; SD, standard deviation**.**

Supplemental Table 8. Adverse events that occurred in ≥1% of all PwHA receiving PK-guided prophylaxis with rurioctocog alfa pegol

Adverse event	FVIII trough level 1-3%, n = 57	FVIII trough level 8-12%, n = 58	All PwHA, N = 115*
Infections and infestations			
Upper respiratory tract infection	6 (10.5)	12 (20.7)	18 (15.7)
Nasopharyngitis	6 (10.5)	5 (8.6)	11 (9.6)
Rhinitis	3 (5.3)	3 (5.2)	6 (5.2)
Influenza	2 (3.5)	1 (1.7)	3 (2.6)
Sinusitis	3 (5.3)	0	3 (2.6)
Tooth abscess	1 (1.8)	1 (1.7)	2 (1.7)
Viral infection	2 (3.5)	1 (1.7)	3 (2.6)
Cellulitis	1 (1.8)	1 (1.7)	2 (1.7)
Gastroenteritis	2 (3.5)	0	2 (1.7)
Impetigo	0	2 (3.4)	2 (1.7)
Injury, poisoning, and procedural complications			
Laceration	2 (3.5)	2 (3.4)	4 (3.5)
Procedural pain	0	2 (3.4)	2 (1.7)
Head injury	2 (3.5)	1 (1.7)	3 (2.6)
Hand fracture	0	2 (3.4)	2 (1.7)
Infusion-related reaction	0	2 (3.4)	2 (1.7)
Radius fracture	2 (3.5)	0	2 (1.7)
Musculoskeletal and connective tissue disorders			
Arthralgia	6 (10.5)	5 (8.6)	11 (9.6)
Back pain	1 (1.8)	3 (5.2)	4 (3.5)
Gastrointestinal disorders			
Diarrhoea	3 (5.3)	2 (3.4)	5 (4.3)
Toothache	1 (1.8)	2 (3.4)	3 (2.6)
Abdominal pain	1 (1.8)	1 (1.7)	2 (1.7)
Nervous system disorders			
Headache	5 (8.8)	6 (10.3)	11 (9.6)
General disorders and all administration site conditions			

Pyrexia	2 (3.5)	3 (5.2)	5 (4.3)
Influenza-like illness	2 (3.5)	1 (1.7)	3 (2.6)
Non-cardiac chest pain	0	2 (3.4)	2 (1.7)
Investigations			
Monocyte count decreased	2 (3.5)	0	2 (1.7)
Alanine aminotransferase increased	1 (1.8)	1 (1.7)	2 (1.7)
Respiratory, thoracic, and mediastinal disorders			
Cough	2 (3.5)	2 (3.4)	4 (3.5)
Oropharyngeal pain	0	2 (3.4)	2 (1.7)
Metabolism and nutrition disorders			
Hypercholesterolemia	1 (1.8)	2 (3.4)	3 (2.6)
Hypertriglyceridemia	1 (1.8)	1 (1.7)	2 (1.7)
Skin and subcutaneous tissue disorders			
Blister	1 (1.8)	1 (1.7)	2 (1.7)
Urticaria	0	2 (3.4)	2 (1.7)
Vascular disorders			
Hypertension	1 (1.8)	1 (1.7)	2 (1.7)
Immune system disorders			
Allergy to arthropod bite	0	2 (3.4)	2 (1.7)

FVIII, factor FVIII; PK, pharmacokinetic; PwHA, people with hemophilia A.

Data represent numbers of patients (%).

*Adverse events that occurred after the first dose of rurioctocog alfa pegol was received post-randomization until study end.

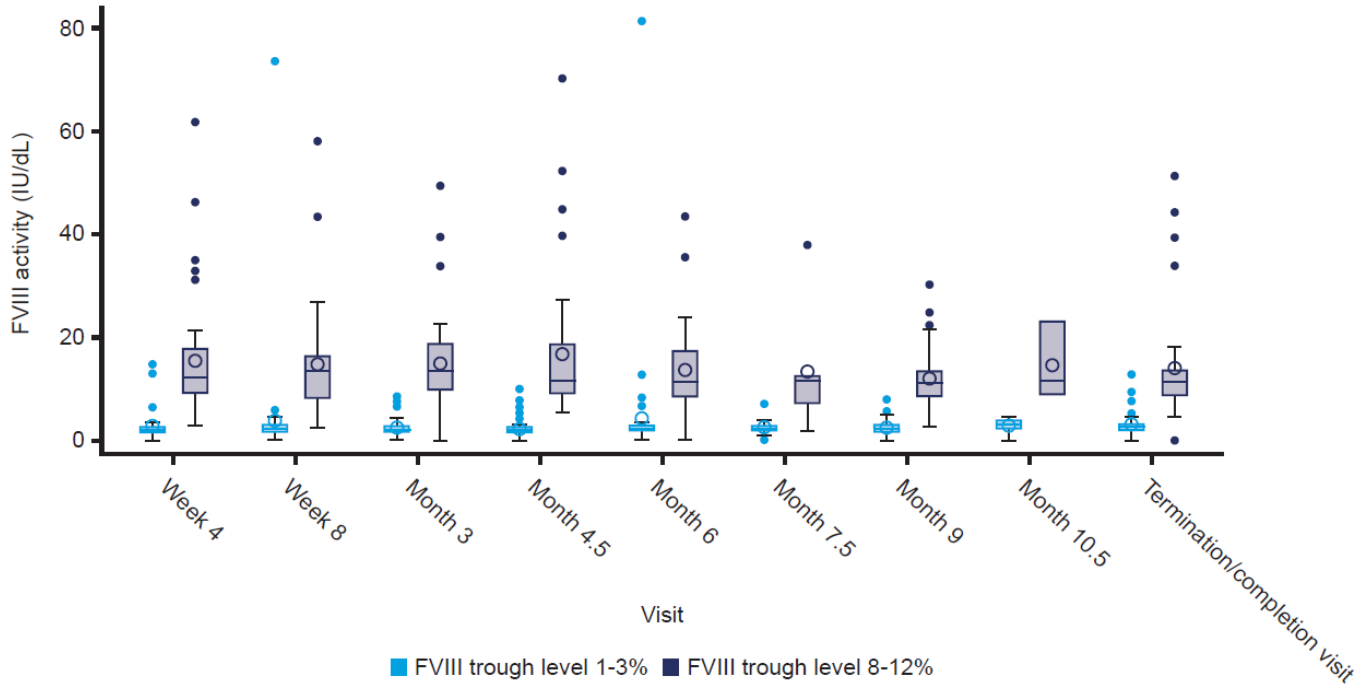
Supplemental Table 9: Average FVIII levels in the first and second 6-month study periods (FAS)

	FVIII trough level 1-3%, n = 57	FVIII trough level 8-12%, n = 58	All PwHA, N = 115*
Average FVIII level in first 6 months, IU/dL			
PwHA, n	48	31	79
Mean (SD)	18.5 (5.5)	36.1 (12.7)	25.4 (12.5)
Median (Q1-Q3)	17.3 (15.2-21.7)	35.0 (29.2-40.9)	22.0 (16.5-32.4)
Average FVIII level in second 6 months, IU/dL			
PwHA, n	48	27	75
Mean (SD)	18.6 (5.7)	33.5 (13.6)	24.0 (11.8)
Median (Q1-Q3)	17.3 (14.5-22.4)	30.9 (24.9-41.2)	20.4 (16.4-28.9)

FVIII, factor VIII; PwHA, people with hemophilia A.

*36 PwHA were excluded because of less robust data available to predict average FVIII levels.

Supplemental figure



Supplemental Figure 1. Calculated plasma FVIII activity trough levels over time by treatment arm (1-stage clotting assay; PK analysis set).

Observed troughs were adjusted to the expected trough level at the end of the planned infusion interval on the basis of infusions recorded in patient diaries.

The box-whisker plots report: min, Q1, median, Q3, max; empty circles represent mean values and filled circles represent the outliers.

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