Supporting Information for (Title): A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management

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1. SUPPORTING STUDY METHODS

1.1 Study Design

A summary of the study procedures and assessments is provided in Supporting Info. Table 1. Dosing for the on-demand treatment of hemorrhages was dependent on the severity and type of bleeding (Supporting Info. Table 2). The hemostatic efficacy of treatment was rated by the subject or site staff using a 4-point ordinal scale (Supporting Info. Table 3).

Subject compliance with treatment was monitored by regularly scheduled telephone calls, an electronic compliance tool provided to the subject and direct review of the subject's source data at the sites and evaluation against the protocol requirements. Drug accountability was evaluated at each interval study visit and at study termination by comparing the infusions recorded in the subject diary, empty vials returned by each subject to the site, and the site's dispensing record.

2. SUPPORTING STUDY RESULTS

2.1 Efficacy results

The mean (range) treatment period of the per-protocol (PP) analysis set was 185 days (137 to 254) for the on-demand regimen, 362 days (283 to 397) for standard prophylaxis, and 361 days (287 to 382) for PK-tailored prophylaxis. Over these periods, a total of 1351 hemorrhages

occurred in 53 subjects who were treated on-demand, 77 hemorrhages in 17 of 30 subjects treated by standard prophylaxis, and 75 hemorrhages in 14 of 23 subjects treated by PK-tailored prophylaxis. No subject treated on-demand was hemorrhage-free during the 6-month treatment period, whereas 13 of 30 and 9 of 23 subjects treated with standard and PK-tailored prophylaxis, respectively (overall 41.5%) experienced no bleeding during the 12-month prophylaxis period.

ABRs for all etiologies (spontaneous and traumatic) and types of bleeding (joint and non-joint) for standard and PK-tailored prophylaxis were similar, and reductions in ABRs compared to on-demand treatment were also similar (Supporting Info. Table 4).

Supporting Info. Table 1 Schedule of study procedures and assessments

Procedure/ assessment	Screening	Part 1 PK		Part 1 and 2 interval study visits[b]	Study termination	
		Pre-infusion[a]	Post-infusion		Pre-infusion[a]	Post-infusion
Informed Consent	X					
Inclusion/Exclusion	X					
Medical History	X					
Interval Medical History				X	X	
Physical Exam	X			X	X	
Vital Signs		X	X			
Clinical Laboratory Assessments	X	X	X	X	X	X
Concomitant Medication	X		X	X		X
AEs			X	X		X
Subject Diary		X		X	X	
HRQoL Questionnaire	X			X		X
Clinical laboratory assessments						
CBC	W	W	W	W	W	
Clinical Chemistry	S	S	S	S	S	
Antibodies to HIV	S					
FVIII Activity	P[g]	P	P	P	P	P
FVIII Inhibitor	P[g]			P	P	
INR	W					
Pregnancy Test	X			X	X	

W, whole blood; S, serum; P, plasma; X, laboratory testing required

Supporting Info. Table 2 rAHF-PFM treatment guidelines during the on-demand period

Type of bleeding	Dose	Frequency of dosing
Superficial bleeding and epistaxis, gum bleeding	10 to 20 IU/kg	Repeat infusions every 12 to 24 hours for 1 to 3 days until the bleed is resolved.
Minor hemarthrosis	20 to 40 IU/kg	Repeat infusions every 12 to 24 hours for 3 days or more until the pain and moderate disability/incapacity are resolved.
Moderate hemarthrosis and deep muscle bleed	30 to 60 IU/kg	Repeat infusions every 12 to 24 hours for 3 days or more until the pain and moderate disability/incapacity are resolved.
Major hemarthrosis or life-threatening hemorrhage	60 to 100 IU/kg	Repeat infusions every 8 to 12 hours until the bleed is resolved.
Genitourinary, gastrointestinal and intracranial episode	60 to 100 IU/kg	Repeat infusions every 8 to 12 hours until the bleed is resolved.

Supporting Info. Table 3 Hemostatic efficacy rating scale for treatment of bleeding

Excellent	Full relief of pain and cessation of objective signs of bleeding (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) within approximately 8 hours of a single infusion. No additional infusion is required for the control of bleeding. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after the infusion. Possibly requires more than 1 infusion for complete resolution.
Fair	Probable or slight relief of pain and slight improvement in signs of bleeding within approximately 8 hours after the infusion. Requires more than 1 infusion for complete resolution.
None	No improvement or condition worsens.

Supporting Info. Table 4 Comparison of annualized bleeding rates (ABRs) between treatment regimens*

		Standard prophylaxis	PK-tailored prophylaxis
All Etiologies, All Types	Median (IQR) ABR	1.0 (3.5)	2.0 (6.9)
	ABR Difference with on-demand†	*P<.0001*	*P<.0001*
	% Reduction with on-demand‡	98.0 (6.7)	95.9 (19.8)
	% Reduction difference with on-demand†	*P<.0001*	*P<.0001*
All Etiologies, Joint Types	Median (IQR) ABR	1.0 (2.1)	2.0 (5.9)
	ABR Difference with on-demand†	*P<.0001*	*P<.0001*
	% Reduction with on-demand‡	97.8 (6.2)	95.8 (19.6)
	% Reduction difference with on-demand†§	*P<.0001*	*P<.0001*
All Etiologies, Non-Joint Types	Median (IQR) ABR	0 (0)	0 (0)
	ABR Difference with on-demand†	*P<.0001*	*P<.0001*
	% Reduction with on-demand‡	100 (2.7)	100 (5.3)
	% Reduction difference with on-demand†	*P<.0001*	*P<.0001*
Spontaneous, All Types	Median (IQR) ABR	0 (1.9)	0 (3.1)
	ABR Difference with on-demand†	*P<.0001*	*P<.0001*
	% Reduction with on-demand‡	100 (5.6)	98.7 (8.9)
	% Reduction difference with on-demand†	*P<.0001*	*P<.0001*
Spontaneous, Joint Types	Median (IQR) ABR	0 (1.6)	0.5 (3.1)
	ABR Difference with on-demand†	*P<.0001*	*P<.0001*
	% Reduction with on-demand‡	100 (3.9)	99.4 (11.4)
	% Reduction difference with on-demand†	*P<.0001*	*P<.0001*
Traumatic, All Types	Median (IQR) ABR	0 (1.0)	1.0 (3.8)
	ABR Difference with on-demand†	*P<.0001*	*P<.0001*
	% Reduction with on-demand‡	100 (5.0)	87.6 (32.0)
	% Reduction difference with on-demand†	*P<.0001*	*P<.0001*
Traumatic, Joint Types	Median (IQR) ABR	0 (1.0)	0.5 (2.0)
	ABR Difference with on-demand†	*P<.0001*	*P<.0001*
	% Reduction with on-demand‡	100 (4.2)	90.8 (31.4)
	% Reduction difference with on-demand†	*P<.0001*	*P<.0001*

* Intention-to-treat analysis set

† Paired difference between on-demand and prophylaxis (Wilcoxon signed-rank test)

‡ Median % reduction in ABRs between on-demand and any prophylaxis