

Supplementary Table S1 Daily FVIII dose by responder type, dosing frequency and dose

Responder type Dosing frequency	Daily dose at ITI start, IU/kg					
	Low dose ^a		High dose ^b		All doses	
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)	<i>N</i>	Mean (SD)
Low responders						
1x/day	1	27.8	8	109.8 (21.7)	9	100.7 (34.0)
2x/day	–	–	3	210.9 (11.1)	3	210.9 (11.1)
3x/week	–	–	1	39.0	1	39.0
3.5x/week	–	–	1	52.6	1	52.6
<i>All frequencies</i>	1	27.8	13	123.3 (57.8)	14	116.4 (61.1)
High responders						
1x/day	20	93.9 (24.0)	4	196.6 (32.4)	24	111.0 (46.3)
2x/day	3	123.9 (16.8)	42	266.5 (77.3)	45	257.0 (82.9)
2x/week	1	16.8	–	–	1	16.8
3x/week	9	28.1 (7.5)	–	–	9	28.1 (7.5)
4x/week	1	44.0	–	–	1	44.0
3.5x/week	6	65.3 (27.9)	–	–	6	65.3 (27.9)
<i>All frequencies</i>	40	73.9 (37.5)	46	260.5 (76.9)	86	173.7 (112.0)
All patients						
1x/day	21	90.7 (27.5)	12	138.7 (49.1)	33	108.2 (43.0)
2x/day	3	123.9 (16.8)	45	262.8 (75.9)	48	254.2 (81.0)
2x/week	1	16.8	–	–	1	16.8
3x/week	9	28.1 (7.5)	1	39.0	10	29.2 (7.9)
4x/week	1	44.0	–	–	1	44.0
3.5x/week	6	65.3 (27.9)	1	52.6	7	63.5 (25.9)
<i>All frequencies</i>	41	72.7 (37.7)	59	230.2 (92.5)	100	165.7 (108.0)

^aLow dose: < 150 IU FVIII/kg/day for high responders, < 50 IU FVIII/kg either daily or every other day for low responders.

^bHigh dose: ≥ 150 IU FVIII/kg/day for high responders, ≥ 50 IU FVIII/kg either daily or every other day for low responders.

Abbreviations: ITI, immune tolerance induction; IU, international units; SD, standard deviation.

Supplementary Table S2 Daily FVIII dose by responder type, dosing frequency and dose in patients who achieved ITI success

Responder type Dosing frequency	Daily dose at ITI start in patients who achieved ITI success ^a , IU/kg					
	Low dose ^b		High dose ^c		All doses	
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)	<i>N</i>	Mean (SD)
<i>Low responders</i>						
1x/day	1	27.8	7	111.7 (22.6)	8	101.2 (36.3)
2x/day	–	–	3	210.9 (11.1)	3	210.9 (11.1)
3x/week	–	–	1	39.0	1	39.0
3.5x/week	–	–	1	52.6	1	52.6
<i>All frequencies</i>	1	27.8	12	125.5 (59.8)	13	118.0 (63.4)
<i>High responders</i>						
1x/day	14	90.5 (25.2)	3	184.6 (26.7)	17	107.1 (44.4)
2x/day	1	117.7	25	268.7 (86.3)	26	262.9 (89.6)
2x/week	–	–	–	–	–	–
3x/week	8	29.2 (7.2)	–	–	8	29.2 (7.2)
4x/week	–	–	–	–	–	–
3.5x/week	6	65.3 (27.9)	–	–	6	65.3 (27.9)
<i>All frequencies</i>	29	69.3 (34.9)	28	259.7 (85.9)	57	162.8 (115.7)
<i>All patients</i>						
1x/day	15	86.3 (29.2)	10	133.6 (41.7)	25	105.2 (41.3)
2x/day	1	117.7	28	262.5 (83.4)	29	257.5 (86.2)
2x/week	–	–	–	–	–	–
3x/week	8	29.2 (7.2)	1	39.0	9	30.3 (7.5)
4x/week	–	–	–	–	–	–
3.5x/week	6	65.3 (27.9)	1	52.6	7	63.5 (25.9)
<i>All frequencies</i>	30	67.9 (35.1)	40	219.5 (100.0)	70	154.5 (109.0)

^aSuccess = Complete success or partial success.

^bLow dose: < 150 IU FVIII/kg/day for high responders, < 50 IU FVIII/kg either daily or every other day for low responders.

^cHigh dose: ≥ 150 IU FVIII/kg/day for high responders, ≥ 50 IU FVIII/kg either daily or every other day for low responders.

Abbreviations: ITI, immune tolerance induction; IU, international units; SD, standard deviation.

Supplementary Table S3 Daily FVIII dose by responder type, dosing frequency and dose in patients who did not achieve ITI success

Responder type Dosing frequency	Daily dose at ITI start in patients who did not achieve ITI success ^a , IU/kg					
	Low dose ^b		High dose ^c		All doses	
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)	<i>N</i>	Mean (SD)
Low responders						
1x/day	–		1	96.2	1	96.2
2x/day	–	–	–	–	–	–
3x/week	–	–	–	–	–	–
3.5x/week	–	–	–	–	–	–
<i>All frequencies</i>	–	–	1	96.2	1	96.2
High responders						
1x/day	6	101.7 (20.9)	1	232.6	7	120.4 (53.0)
2x/day	2	127.0 (22.5)	17	263.3 (64.1)	19	249.0 (74.3)
2x/week	1	16.8	–	–	1	16.8
3x/week	1	19.3	–	–	1	19.3
4x/week	1	44.0	–	–	1	44.0
3.5x/week	–	–	–	–	–	–
<i>All frequencies</i>	11	85.8 (43.0)	18	261.6 (62.6)	29	195.0 (102.8)
All patients						
1x/day	6	101.7 (20.9)	2	164.4 (96.5)	8	117.4 (49.8)
2x/day	2	127.0 (22.5)	17	263.3 (64.1)	19	249.0 (74.3)
2x/week	1	16.8	–	–	1	16.8
3x/week	1	19.3	–	–	1	19.3
4x/week	1	44.0	–	–	1	44.0
3.5x/week	–	–	–	–	–	–
<i>All frequencies</i>	11	85.8 (43.0)	19	252.9 (71.7)	30	191.7 (102.6)

^aSuccess = Complete success or partial success.

^bLow dose: < 150 IU FVIII/kg/day for high responders, < 50 IU FVIII/kg either daily or every other day for low responders.

^cHigh dose: ≥ 150 IU FVIII/kg/day for high responders, ≥ 50 IU FVIII/kg either daily or every other day for low responders.

Abbreviations: ITI, immune tolerance induction; IU, international units; SD, standard deviation.

Supplementary Table S4 Mean (SD) monthly bleeding rates during ITI in patients who achieved success and non-success patients

BE severity Dose group	Non-success patients (n = 30)	ITI success ^a patients (n = 70)	
		Prior to negative inhibitor	After negative inhibitor
<i>All BEs</i>			
All patients	0.53 (0.88)	0.39 (0.65)	0.07 (0.13)
Low-dose patients ^b	0.38 (0.35)	0.34 (0.42)	0.09 (0.18)
High-dose patients ^c	0.61 (1.07)	0.43 (0.79)	0.05 (0.08)
<i>Mild BEs</i>			
All patients	0.15 (0.18)	0.35 (0.60)	0.07 (0.11)
Low-dose patients ^b	0.07 (0.04)	0.18 (0.24)	0.07 (0.13)
High-dose patients ^c	0.21 (0.22)	0.52 (0.78)	0.06 (0.07)
<i>Moderate BEs</i>			
All patients	0.34 (0.52)	0.30 (0.37)	0.04 (0.05)
Low-dose patients ^b	0.23 (0.21)	0.33 (0.34)	0.03 (0.03)
High-dose patients ^c	0.41 (0.65)	0.27 (0.39)	0.04 (0.06)
<i>Severe BEs</i>			
All patients	0.19 (0.30)	0.12 (0.14)	0.01 (0.02)
Low-dose patients ^b	0.16 (0.15)	0.12 (0.10)	0.01 (0.01)
High-dose patients ^c	0.20 (0.36)	0.12 (0.17)	0.02 (0.02)

^aComplete success or partial success.

^bLow dose: < 150 IU/kg/day for high responders, < 50 IU/kg either daily or every other day for low responders.

^cHigh dose: ≥ 150 IU/kg/day for high responders, ≥ 50 IU/kg either daily or every other day for low responders.

Abbreviations: BE, bleeding episode; ITI, immune tolerance induction.

Supplementary Figure S1 Proportion of patients achieving ITI success by 9 or 12 months or at any time from start of ITI. (A) overall population ($n = 100$), (B) patients who achieved success ($n = 70$).

