Recombinant Factor VIII Fc Fusion Protein for First-time Immune Tolerance Induction: Final Results of the verITI-8 Study

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Supplement

Supplemental Methods:

Supplemental Table 1: Sites and investigators in the verITI-8 study

Site	Investigator
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McMaster Children's Hospital, Hamilton, ON, Canada	Anthony Chan
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Azienda Ospedaliera Pediatrica Santobono Pausillipon, Naples, Italy	Michele Schiavulli
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Fondazione IRCCS CA' Granda Ospedale Maggiore Policlinico, Milan, Italy	Flora Peyvandi
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UZ Leuven, Leuven, Belgium	Kathelijne Peerlinck
Groupement Hospitalier Est- Hôpital Louis Pradel, Bron, Rhone, France	Claude Negrier
Universitaetsklinikum Bonn AoeR, Bonn, Nordrhein Westfalen, Germany	Johannes Oldenburg
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Hôpital de la Timone, Marseille, Bouches-du-Rhône, France	Herve Chambost
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Rush University Medical Center, Chicago, Illinois, USA	Mindy Simpson
Michigan State University, East Lansing, Michigan, USA	Roshni Kulkarni
Children's Hospital Los Angeles, Los Angeles, California, USA	Guy Young
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El Paso Children's Hospital, El Paso, Texas, USA	Ranjan Bista
Cook Children's Medical Center, Fort Worth, Texas, USA	Timothy McCavit

Additional exclusion criteria included:

- History of hypersensitivity or anaphylaxis with any factor VIII
- Planned major surgery scheduled during the study unless deferred until after study completion (minor surgeries such as dental procedures or central venous access device placement/replacements were allowed)
- Abnormal renal function (serum creatinine >1.5 mg/dL or 2× upper limit of normal [ULN])
- Serum alanine aminotransferase or aspartate aminotransferase >5× ULN
- Serum total bilirubin >3× ULN
- Concurrent systemic immunosuppressant treatment within 12 weeks prior to screening (excepting ribavirin for treatment of hepatitis C and/or systemic steroids [total of 2 courses of pulse treatments lasting no more than 7 days within 12 weeks prior to study Day 1] and/or inhaled steroids)
- High risk of cardiovascular, cerebrovascular, or other thromboembolic events as judged by the investigator
- If known as HIV positive, then CD4 lymphocytes <200 mm^3 or viral load >400 copies/mL at screening
- Current enrollment or a plan to enroll in any interventional clinical study in which an investigational treatment or approved therapy, other than recombinant factor VIII Fc fusion protein, for investigational use is administered within 30 days (or 5 half-lives of the agent, whichever is longer) prior to the baseline visit
- Inability to comply with study requirements
- Presence of condition or laboratory result that may interfere with a subject's ability to comply with protocol requirements
- Any other reason that, in the opinion of the investigator, would make a subject unsuitable for enrollment

Supplementary Table 2. Individual ITI statuses

Patient	Race	*F8* genotype	Previous treatment	Historical peak inhibitor titer, BU/mL*	Inhibitor titer at start of ITI, BU/mL	Time from inhibitor diagnosis to start of ITI, weeks	Time to, weeks (from start of ITI)			Inhibitor titer at end, BU/mL	Time on study, weeks
							Negative inhibitor titer[†]	Normal IR	$t_{½}$ ≥7 hrs		
Success[‡, §]											
1	White	Large structure change (Intron-1 inversion)	rFVIII (OD)	14.1	9	12.1	2.3	4.3	8.1	-	59.7
2	White	Large structure change (Intron-22 inversion)	rFVIII (PPX)	10	3	16.7	2.1	4.1	8.1	-	61.8
3	White	Small structure change (in-frame deletion)	pdFVIII (PPX)	8.11	0.71	18. 8	2.3	6.8	9.8	-	60. 1
4	White	Large structure change (Intron-22 inversion)	rFVIII (PPX)	9	3.25	71.6	2.3	6.0	10.3	-	68.6
5	White	Large structure change (Intron-22 inversion)	rFVIII (PPX)	6.2	0.8	28.3	1.7	5.4	11.4	-	61.2
6	White	Large structure change (Intron-22 inversion)	pdFVIII (OD)	40	2	744.9	1.7	6.0	12.0	-	65.5
7	Black	Nonsense (substitution)	rFVIII (PPX)	19.2	11	20.4	14.1	16.1	18.2	-	72.5
8	White	Large structure change (Intron-22 inversion)	rFVIII (PPX)	25.6	10.4	11.5	20.1	22.4	26.2	-	78.3
9	White	Frameshift (deletion)	pdFVIII (PPX)	7.1	20	3.8	15.5	28.1	31.9	-	82.9

10	White	Nonsense (substitution)	rFVIII (PPX)	11.3	5.1	23.1	38.2	41.9	49.8[¶]	-	121.7
Partial success[‖]											
11	Black	Large structure change (Intron-22 inversion)	rFVIII (PPX)	150	4.2	>202	12.5	14.1	-	2	53.1
ITI failure											
12	White	-	rFVIII (PPX)	132.2	94	4.1	-	-	-	194.5	41
13	White	Large structure change (Intron-22 inversion)	rFVIII (PPX)	256	25	55.5	-	-	-	1280	42.1
14	White	Large structure change (deletion)	rFVIII (PPX)	105	12.2	63. 8	-	-	-	458.1	52.4
15	Other	Large structure change (deletion)	pdFVIII (OD), rFVIII (PPX)	232	144	64.4	-	-	-	608	54. 7
16	Other	Frameshift (deletion)	pdFVIII (OD), rFVIII (OD)	48	40	70.9	40.2	-	-	<0.6	55.4

BU, Bethesda unit; IR, incremental recovery; ITI, immune tolerance induction; OD, on demand; pdFVIII, plasma-derived factor VIII; PK, pharmacokinetic; PPX, prophylaxis; rFVIII, recombinant factor VIII; $t_{½}$, half-life.

*Prestudy value.

[†]Defined as time to first negative inhibitor titer recorded.

[‡]No relapses were observed during the study for patients who were successfully tolerized.

[§]All patients who were successfully tolerized had an ending inhibitor titer of <0.6 BU/mL.

[‖]Achieved negative inhibitor titer and 1 of the PK parameters of ITI success.

[¶]The subject underwent a washout procedure that delayed final $t_{½}$ measurement but was considered a success.

Supplementary Table 3: Summary of initial tapering doses, last prescribed tapering dose, and last prescribed prophylactic dose during follow-up

n (%)	Patients who were successful with rFVIIIFc ITI (n=10)
Initial tapering dose and dosing frequency*,†	
100 IU/kg QD	5 (50.0)
100 IU/kg QOD	1 (10.0)
111 IU/kg QD	1 (10.0)
125 IU/kg QD	1 (10.0)
130 IU/kg QD	1 (10.0)
200 IU/kg QD	1 (10.0)
Last prescribed tapering dose and dosing frequency*	
50 IU/kg QOD	3 (30.0)
50 IU/kg 3×/week	1 (10.0)
50 IU/kg Q3D	1 (10.0)
59.6 IU/kg QOD	1 (10.0)
60 IU/kg QOD	1 (10.0)
75 IU/kg QOD	2 (20.0)
200 IU/kg QOD	1 (10.0)
Last prescribed prophylactic dose and dosing frequency‡,§	
47 IU/kg 3×/week	1 (10.0)
50 IU/kg QOD	1 (10.0)
50 IU/kg 3×/week	2 (20.0)
50 IU/kg Q3D	1 (10.0)
60 IU/kg 3×/week	1 (10.0)
63.5 IU/kg QOD	1 (10.0)
75 IU/kg QOD	2 (20.0)
150 IU/kg QOD	1 (10.0)

QD, every day; Q3D, every 3 days; QOD, every other day.

*Tapering period full analysis set. †Initial tapering dose and dosing frequency is defined as the first dose of rFVIIIFc during the tapering period. ‡Follow-up period full analysis set. §Last prescribed prophylactic dose is defined as the last prescribed dose of the follow-up period.

Supplementary Table 4. Adherence based on the prescribed daily dose of rFVIIIFc in the ITI full analysis set*

	Total[†] (N=16)	**ITI period[†] (N=16)**	**Tapering period[‡] (N=10)**	**Follow-up period[§] (N=10)**
Median (%)	101.9	101.7	107.5	97.4
IQR	96.3–105.6	95.4–105.6	104.7–113.9	94.5–106.2
Range	83.7–113.2	83.7–119.5	98.0–115.4	70.1–121.5

IQR, interquartile range; ITI, immune tolerance induction; rFVIIIFc, recombinant factor VIII Fc fusion protein.

*Adherence was based on prescribed daily dose for the total, ITI, tapering, or follow-up periods defined as the percentage of administered doses versus the prescribed doses for a patient for that treatment period.

[†]Total study and ITI period based on the ITI full analysis set.

[‡]Tapering period is based on the tapering period full analysis set.

[§]Follow-up period is based on the follow-up period full analysis set.

Supplementary Table 5. Bypassing agent use during the ITI period

Patient	ITI outcome	Annualized total consumption IU/kg/year*, †, ‡	
		aPCC	rFVIIa
1	Success	-	-
2	Success	-	-
3	Success	-	-
4	Success	0	0
5	Success	0	0
6	Success	0	714.1
7	Success	0	0
8	Success	0	0
9	Success	0	5691.0
10	Success	0	539.3
11	Partial success	0	0
12	Treatment failure	0	47,267.8
13	Treatment failure	43,410.7	0
14	Treatment failure	153.5	23,641.7
15	Treatment failure	9463.0	0
16	Treatment failure	0	0

aPCC, activated prothrombin complex concentrate; ITI, immune tolerance induction; rFVIIa, recombinant activated factor VII.

*Bypassing agents were used only during the ITI period. †Annualized analysis excludes patients who were observed for <90 days in the period; those patients are indicated with a "–"and 1 such subject received bypassing agents. ‡Annualized consumption is the (total consumption/length of period in days) × 365.25.

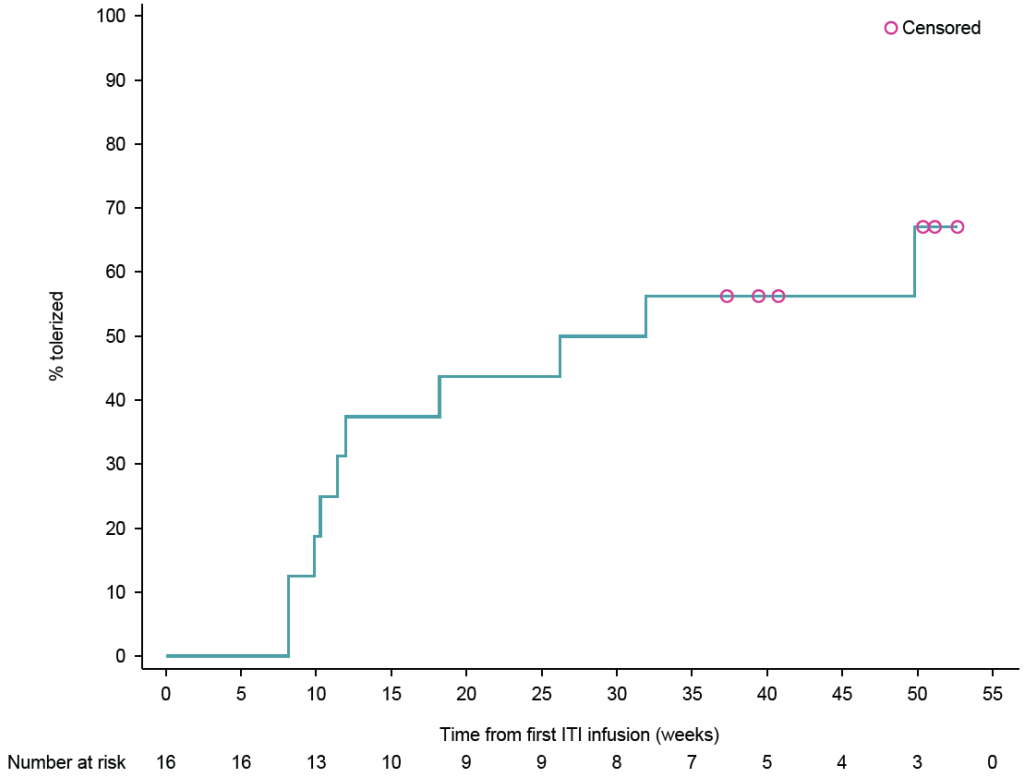
Supplementary Table 6. Most common TEAEs (occurring in ≥15% of subjects)

Preferred term, n (%)	**Overall (N=16)**
Pyrexia	7 (43.8)
Nasopharyngitis	5 (31.3)
Iron deficiency anemia	4 (25.0)
Vascular device infection	4 (25.0)
Viral upper respiratory tract infection	4 (25.0)
Eczema	4 (25.0)
Diarrhea	3 (18.8)
Vomiting	3 (18.8)
Cough	3 (18.8)
Pharyngeal erythema	3 (18.8)
Rhinorrhea	3 (18.8)

N, number of subjects; n (%), number and percent of subjects with at least 1 TEAE for each preferred term. Patients were counted once if they reported multiple events of the same preferred term.

TEAE, treatment-emergent adverse event.

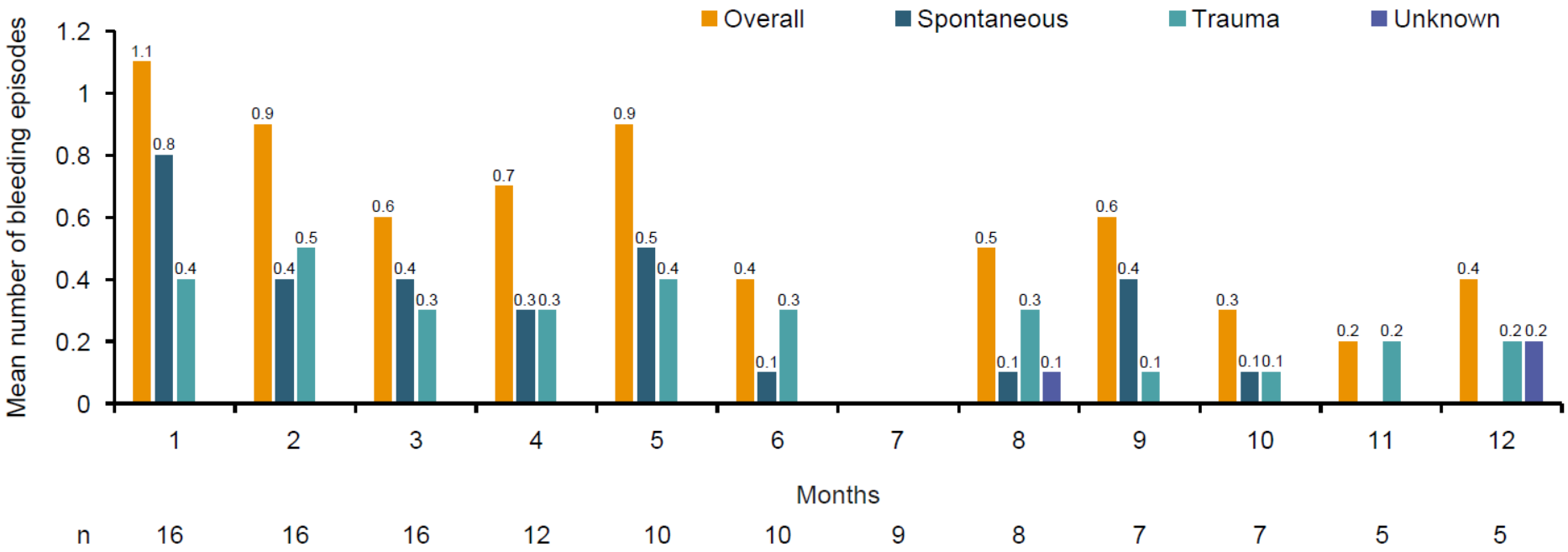
Supplementary Figure 1. Kaplan–Meier plot of time to tolerization in the ITI full analysis set (weeks) [*, †]



BU, Bethesda unit; IR, incremental recovery; ITI, immune tolerance induction; $t_{½}$, half-life.

[*]Subjects not achieving ITI success during the ITI period (48 weeks) were censored at the latest time with positive inhibitor titer data for this analysis. The 6 patients censored completed the 48-week ITI period without tolerizing. [†]Reaching tolerization (success) was defined as meeting all 3 prespecified criteria of a negative inhibitor titer of <0.6 BU/mL at 2 consecutive determinations, normal IR at 2 consecutive determinations, and $t_{½}$ ≥7 hours within 48 weeks of ITI treatment.

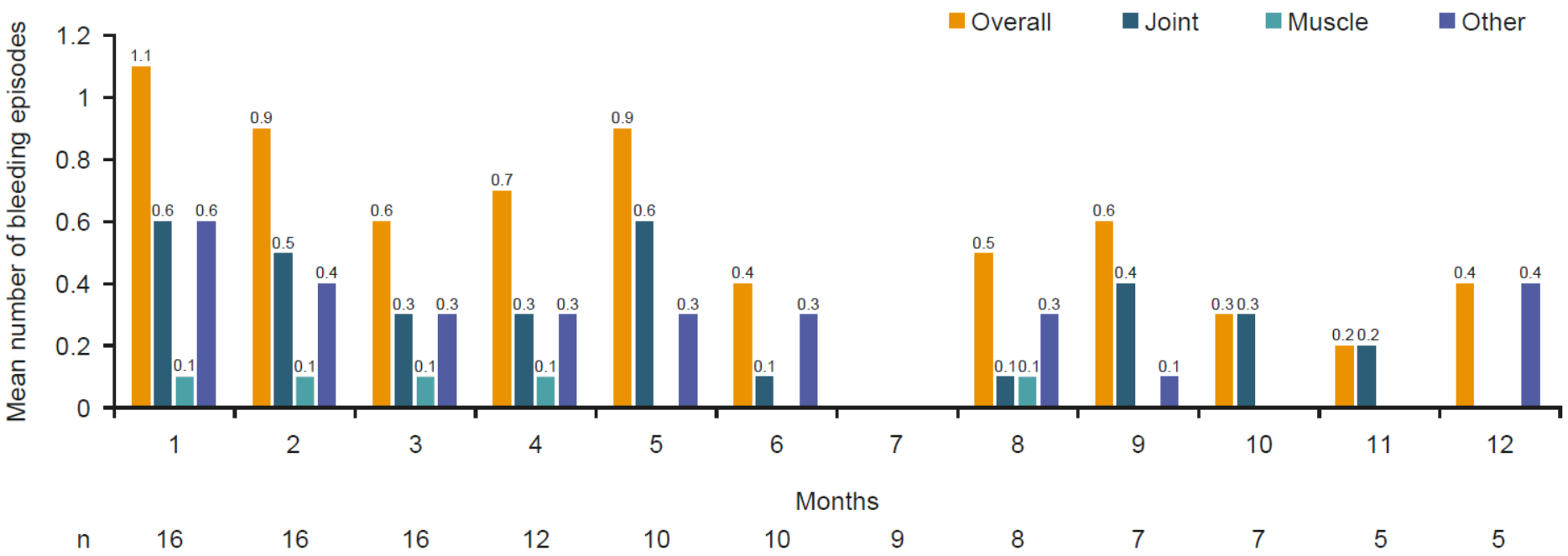
Supplementary Figure 2. Bleeding episodes during ITI period (per month by type)*



ITI, immune tolerance induction.

*Number of bleeds per month for a patient during the ITI period is defined as the number of bleeds in each month (30.4 days) during the ITI period.

Supplementary Figure 3. Bleeding episodes during ITI period (per month by location)*



ITI, immune tolerance induction.

*Number of bleeds per month for a patient during the ITI period is defined as the number of bleeds in each month (30.4 days) during the ITI period.