Supplementary supporting information

Title: Comparative effectiveness of valoctocogene roxaparvovec and efanesoctocog alfa in the treatment of severe hemophilia A: A matching-adjusted indirect comparison of bleeding frequency

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Table S1: Summary of bleeding definitions between GENEr8-1 and XTEND-1, with key differences to note

XTEND-1 bleeding episodes definition[a]	GENEr8-1 bleeding definition[b]	Comparison
All primary analyses in XTEND-1 were based on ISTH criteria for treated bleeding episodes using a standardized definition, as follows: • A bleeding episode starts from the first sign of bleeding and ends no more than 72 hours after the last injection to treat the bleeding episode. • Any subsequent bleeding at the same location and injections administered less than or equal to 72 hours from the previous injection will be considered the same bleeding episode. • Multiple bleeding locations treated with a single injection will also be considered a single bleeding episode. Any injection to treat the bleeding episode that is administered more than 72 hours after the preceding one will be considered the first injection to treat a new bleeding episode in the same location. • Any injection used to treat subsequent bleeding at a different location will be considered a separate bleeding episode, regardless of the time from the last injection to treat a bleeding episode.	The criteria for treated bleeds in GENEr8-1 were: • A bleed directly followed by a hemophilia medication reported to be a "treatment for bleed" within 72 hours (or 3 calendar days if time is not available) is considered to be a treated bleed. This bleed and the first treatment thereafter are referred to as a pair. • Two bleeds of the same type and at the same anatomical location are considered to be one bleed if the second occurs within 72 hours (or 3 calendar days if time is not available) from the last treatment for the first bleed. The last treatment is defined as the last treatment before a new bleed occurs, either in the same or in a different location. This is regardless of whether the second bleed is followed by a treatment. • If multiple bleeds of different type or/and different anatomical location occur within 24 hours (of the last bleed before treatment for bleed) or on the same calendar day, the subsequent treatment within 72 hours (or 3 calendar days if time is not available) is considered to pair with each of these bleeds. Each of these bleeds that is within 72 hours (or 3 calendar days if	• Bleeding at the same anatomical location is defined similarly between the trials, with both requiring a second bleed to occur within 72 hours of the last treatment to treat the previous bleed. • The key difference between the trials is that bleeding at different anatomical locations are counted as individual bleeds in GENEr8-1 but are considered as 1 treated bleeding episode in XTEND-1. ○ For example, if a patient has bleeding at 5 different locations and are treated with 1 injection, then this would equal 5 treated bleeds in GENEr8-1 as opposed to 1 treated bleeding episode in XTEND-1. ○ In both trials, if bleeding then persisted in the same location >72 hours after the last injection to treat the prior bleed, then this would be treated as a new bleed.

	time is not available) of the subsequent treatment is therefore considered to be a treated bleed.	

Key: [a] Bleeding definitions for XTEND-1 were taken from supplementary material in the clinical trial publication (14)

[b] Bleeding definitions were taken from the clinical study report from GENEr8-1 (6–9)

Figure S1: Histogram of patient MAIC weightings following reweighting in the primary analysis; matching on mean treated ABR and the proportion of patients experiencing zero treated bleeds

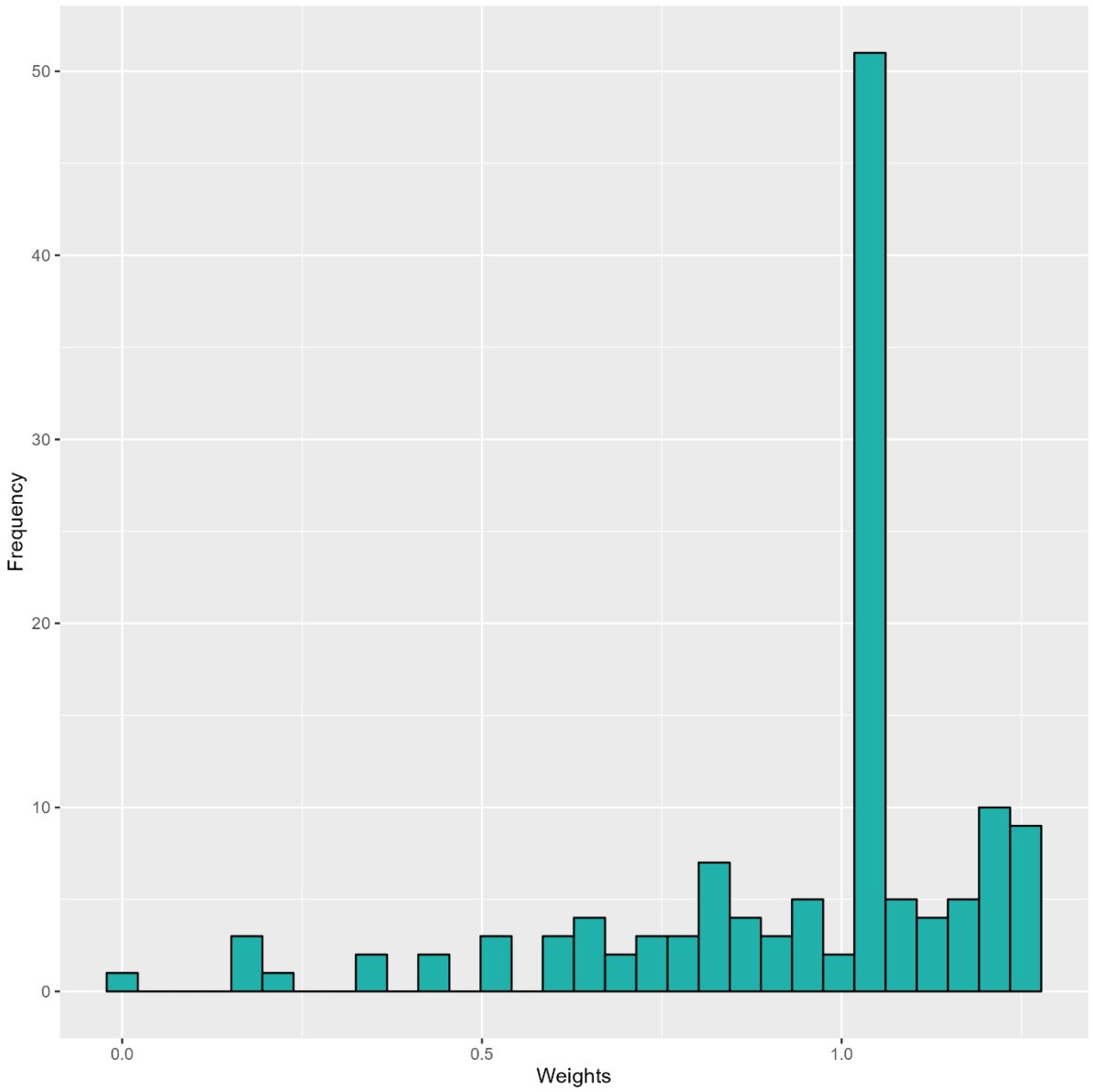

Table S2: Summary of patient characteristics and outcomes following sensitivity analyses, matching on different combinations of baseline characteristics

Characteristic	XTEND-1 Group A	PLD unweighted	Match 1 (Primary)	Match 2	Match 3	Match 4	Match 5	Match 6	Match 7	Match 8	Match 9
N Patients	133	132	132	132	132	132	132	132	132	132	132
ESS	-	-	123.0	123.5	98.8	123.9	122.6	92.2	92.0	93.9	92.1
ESS (%)	-	-	93	94	75	94	93	70	70	71	70
Baseline characteristics											
Mean treated ABR	3.2	5.4	3.2*	3.2*	5.2	3.7	3.2*	3.2*	3.2*	3.7	3.2*
% 0 Bleeds in the prior 12 months to baseline	36.1	32.6	36.1*	40.0*	31.4	36.1*	36.1*	38.0*	36.1*	36.1*	36.1*
Mean age	33.9	31.4	31.8*	31.5*	33.9*	31.7*	31.8*	33.9*	33.9*	33.9*	33.9*
Mean VWF	115.9	108.4	110.1*	109.8*	115.9*	109.6*	110.1*	115.9*	115.9*	115.9*	115.9*
% 0 Target joints at baseline	80.5	89.4	91.2	91.2	80.5*	90.9	91.2	80.5*	80.5*	80.5*	80.5*
% White race	53.4	71.2	70.7	70.4	53.4*	69.7	70.2	53.4*	53.4*	53.4*	53.4*
% >10 Bleeds in the 12 months prior to baseline	6.0	15.2	7.1	7.7	13.0	6.0*	6.0*	6.5*	6.2*	6.0*	6.0*
Outcomes											
Mean treated ABR	0.71	0.86	0.79	0.77	0.90	0.77	0.78	0.83	0.84	0.83	0.84
% 0 treated bleeds	64.7	81.1	83.1	83.1	79.3	83.3	83.3	81.3	81.1	81.2	81.2

Grey fill = The variable was not matched on at baseline.

Key: *The value of a variable is within 10% of the comparators value for the same variable

Abbreviations: ABR, annualized bleed rate; ESS, effective sample size; PLD, patient-level data; VWF, Von Willebrand factor