Comparative effectiveness of valoctocogene roxaparvovec and prophylactic factor VIII replacement estimated through propensity scoring

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Disclosures for Anthony Hatswell

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Research Support / PI	No relevant conflicts of interest to declare
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Speakers Bureau	No relevant conflicts of interest to declare
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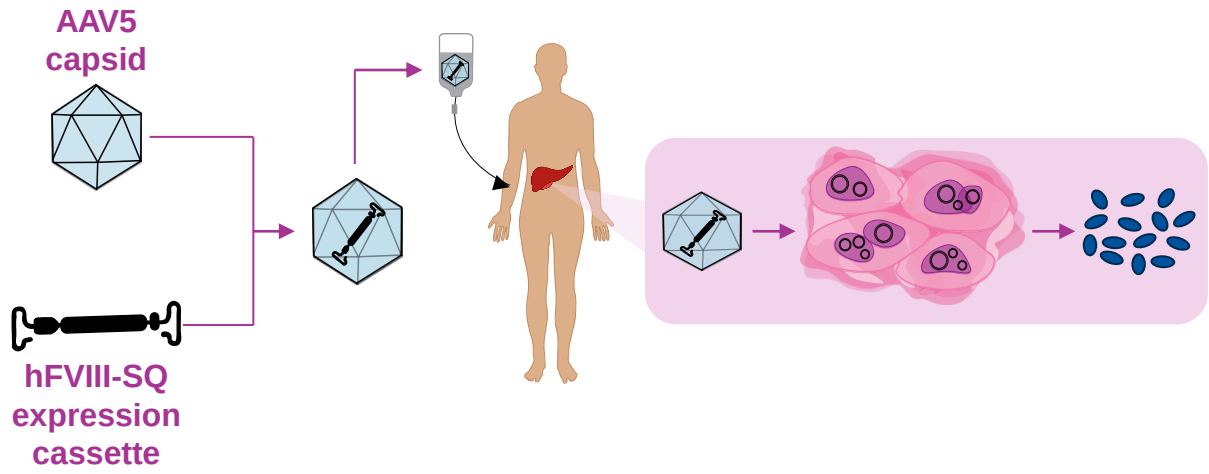
Scientific Advisory Board	No relevant conflicts of interest to declare

Valoctocogene roxaparvovec gene therapy for severe hemophilia A

- Valoctocogene roxaparvovec is a replication incompetent, adeno-associated virus serotype 5 vector that encodes for a B-domain–deleted form of human FVIII
- Valoctocogene roxaparvovec is being investigated in Phase 1/2 and Phase 3 trials in patients with severe HA, with over 6 years of data to date[1,2]
- In the Phase 3 GENEr8-1 trial, bleeding outcomes in n = 112 valoctocogene roxaparvovec-infused participants, who rolled over from a prospective noninterventional study, were superior to FVIII prophylaxis at baseline[2]



Outcomes in GENEr8-1, rollover population[2]	Baseline	Year 1 datacut
Mean ABR (treated bleeds/year)	4.8	0.8
Participants with zero treated bleeds (%)	32%	80%

AAV5, adeno-associated virus serotype 5; ABR, annualized bleeding rate; FVIII, factor VIII; HA, hemophilia A; hFVIII-SQ, B-domain–deleted human FVIII.

1) Pasi et al. *Haemophilia*. 2021;27(6):947–56. 2) Ozelo et al. *N Engl J Med*. 2022;386(11):1013–25.

Aims and methods

Aim: To compare bleeding outcomes among PwSHA treated with valoctocogene roxaparvovec vs prophylactic FVIII replacement, accounting for differences in observed baseline characteristics

Time horizons

- Intervention[1]
  - **From** week 5 post valoctocogene roxaparvovec administration
  - **To** last visit at data cut off (range 358–659 days)
- Control[2]
  - **From** week 0
  - **To** end of follow-up in NIS (range 171–427 days)

Outcomes: Intervention vs control

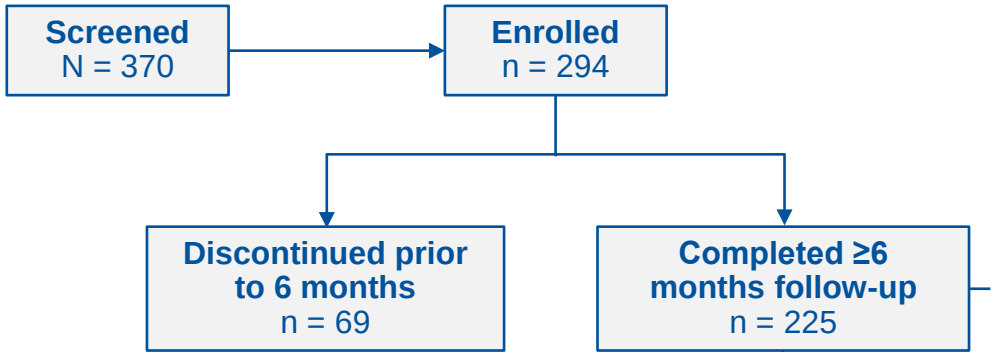
- Treated bleeds
  - Mean ABR
  - Proportion of participants with zero bleeds
- All bleeds
  - Mean ABR
  - Proportion of participants with zero bleeds

ABR, annualized bleeding rate; FVIII, factor VIII; NIS, noninterventional study; PwSHA, persons with severe hemophilia A.
1) Ozelo et al. *N Engl J Med*. 2022;386(11):1013–25; 2) Kenet et al. *J Clin Med*. 2021;10:5959.

Study populations

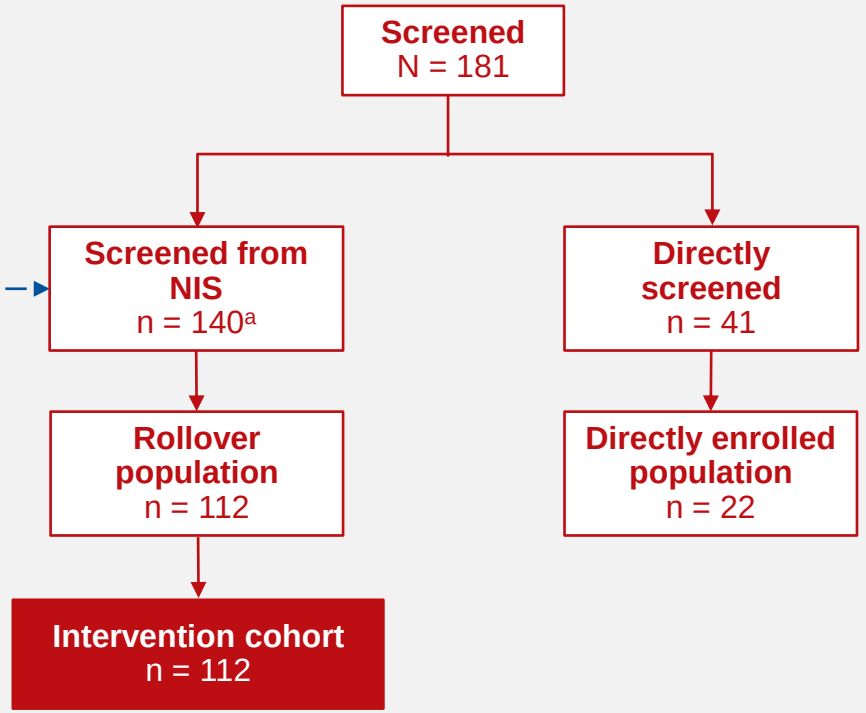
Noninterventional study[1]

- Prospective, multicenter, multinational, longitudinal study of PwSHA receiving prophylactic FVIII



GENEr8-1 (NCT03370913)[2]

- Open-label, single-group, multicenter, Phase 3 trial evaluating the safety and efficacy of valoctocogene roxaparvovec in PwSHA



[a]3 participants screened from the NIS for GENEr8-1 did not complete ≥6 months follow-up; however, none of the 3 were dosed.
AAV5, adeno-associated virus serotype 5; FVIII, factor VIII; NIS, noninterventional study; PwSHA, persons with severe hemophilia A.
1) Kenet et al. *J Clin Med*. 2021;10:5959. 2) Ozelo et al. *N Engl J Med*. 2022;386(11):1013–25.

Methods (propensity scoring)

- Propensity scores (PS) control for potential differences in baseline characteristics between cohorts[1]
- Characteristics included in the PS
  - Clinically related to ABR
  - Statistically related to ABR
    - Stepwise regression
    - Dependent variable: NIS on-study ABR
- Standardized mortality ratio weighting (SMRW) was used to re-weight the control cohort to match baseline characteristics in the intervention cohort

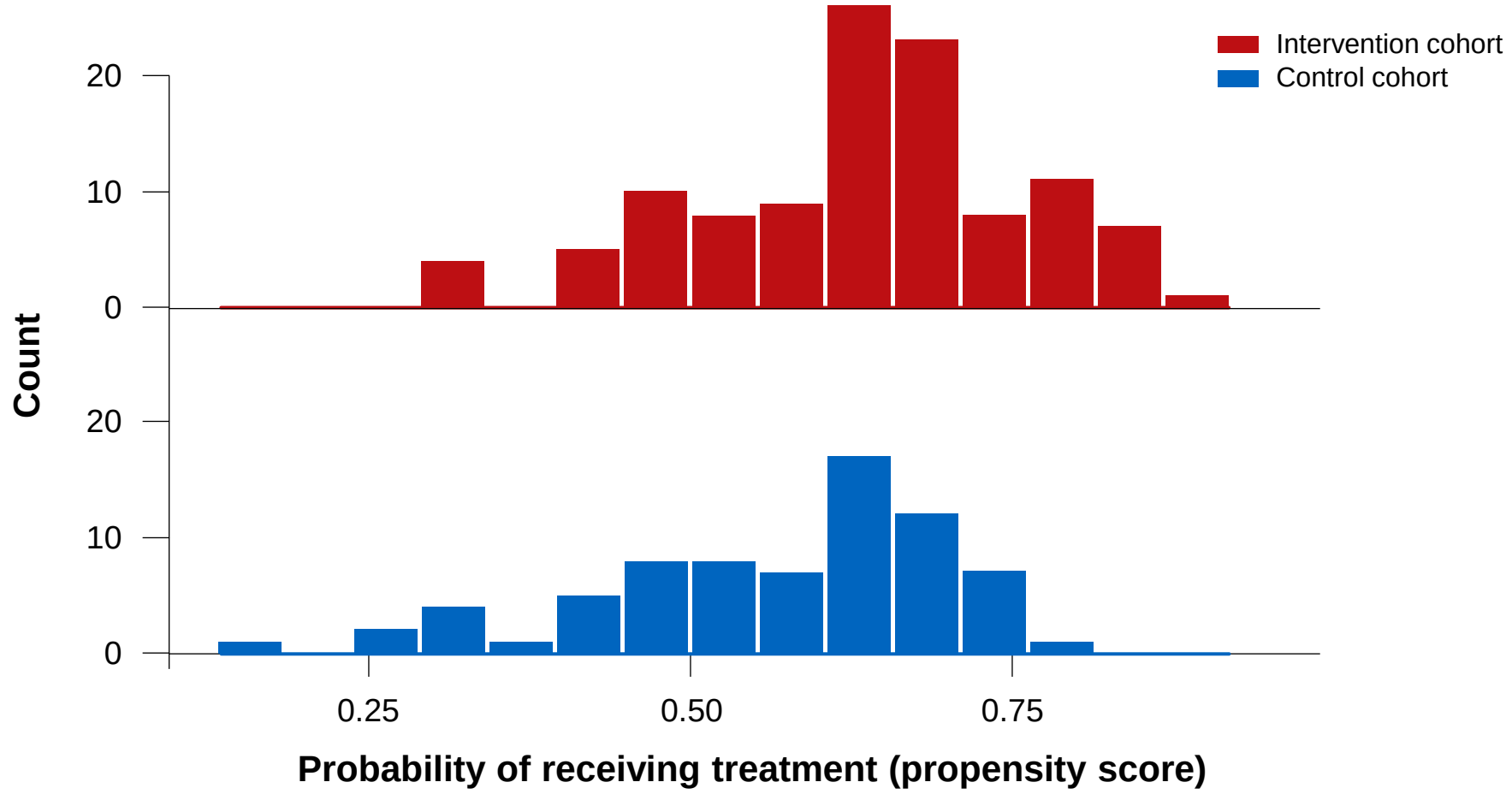
Baseline characteristics used to inform the propensity scores
Age, years
BMI, kg/m^2 (≥30)*
Problem joint, >0 (yes vs no)*
Region (Africa, Asia, South America)*
Prior FVIII treatment, EHL (yes vs no)*
Baseline IU/kg/year
Baseline ABR (treated bleeds)*

*Characteristics identified in stepwise regression.

ABR, annualized bleeding rate; BMI, body mass index; EHL, extended half-life; FVIII, factor VIII; NIS, noninterventional study.

1) Austin. *Multivar Behav Res*. 2011;46:399–424.

Distribution of propensity scores pre-SMRW by treatment group



SMRW, standardized mortality ratio weighting.

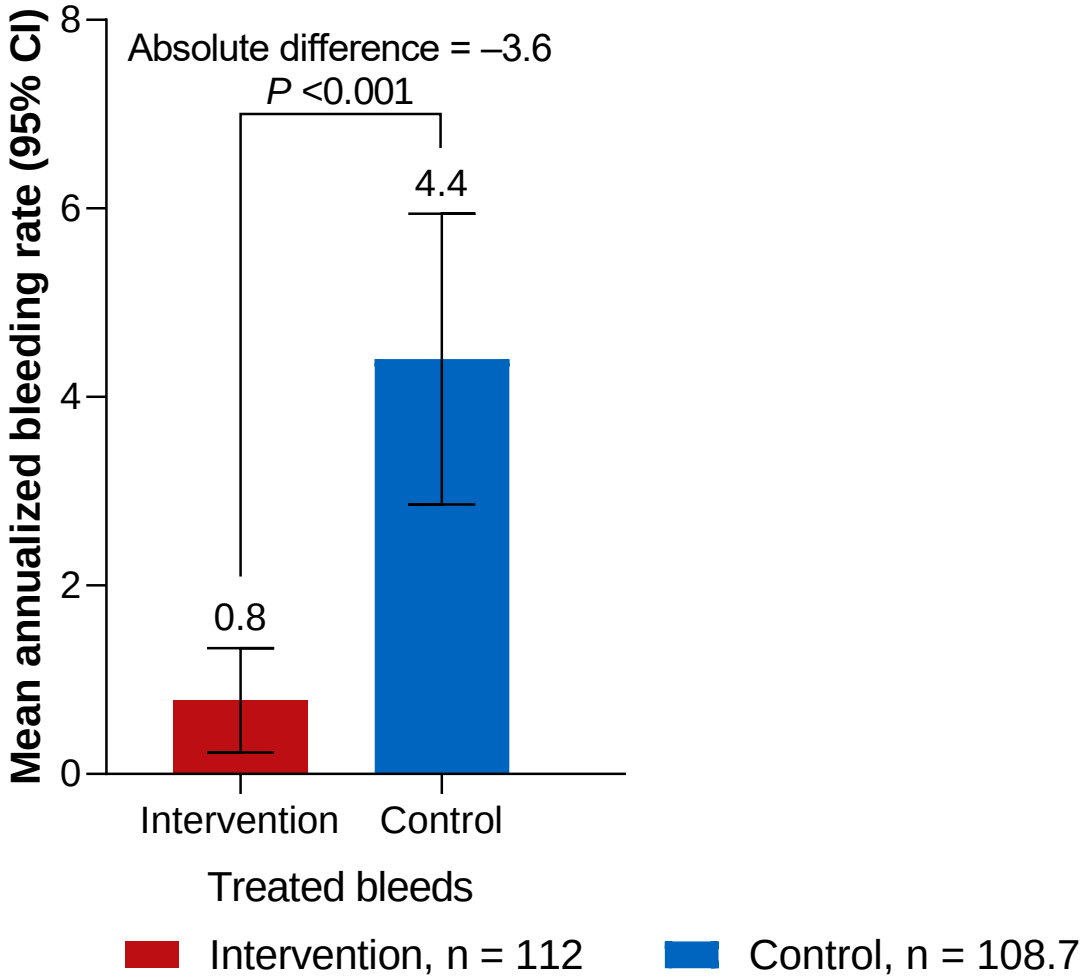
Baseline characteristics included in the propensity score pre- and post-SMRW

Baseline characteristics	Pre-weighting			Post-weighting		
	Intervention	Control	SMD	Intervention	Control	SMD
n (sample)	112	73		112	108.7	
Age, years, mean (SD)	31.8 (10.7)	36.1 (14.2)	**0.344**	31.8 (10.7)	32.1 (11.8)	**0.022**
BMI, kg/m^2 (≥30), n (%)*	15 (13.4)	15 (20.5)	**0.191**	15.0 (13.4)	16.7 (15.4)	**0.056**
Problem joint, >0, n (%)*	30 (26.8)	24 (32.9)	**0.133**	30.0 (26.8)	28.1 (25.9)	**0.021**
Region = Africa, n (%)*	16 (14.3)	11 (15.1)	0.022	16.0 (14.3)	13.1 (12.1)	**0.066**
Region = Asia, n (%)*	11 (9.8)	7 (9.6)	0.008	11.0 (9.8)	10.3 (9.5)	**0.012**
Region = South America, n (%)*	19 (17.0)	12 (16.4)	0.014	19.0 (17.0)	22.2 (20.4)	**0.089**
Prior FVIII treatment – EHL, n (%)*	29 (25.9)	30 (41.1)	**0.326**	29.0 (25.9)	33.4 (30.8)	0.108
Baseline IU/kg/year, mean (SD)	3857 (1834)	3827 (1699)	0.017	3857 (1834)	3880 (1654)	**0.013**
Baseline ABR (treated bleeds), mean (SD)*	5.9 (11.7)	4.0 (5.3)	**0.207**	5.9 (11.7)	4.2 (5.2)	0.189

*Characteristics identified in stepwise regression.
ABR, annualized bleeding rate; BMI, body mass index; EHL, extended half-life; FVIII: factor VIII; SD, standard deviation; SMD, standardized mean difference; SMRW, standardized mortality ratio weighting.

Results: Mean annualized bleeding rate (ABR)

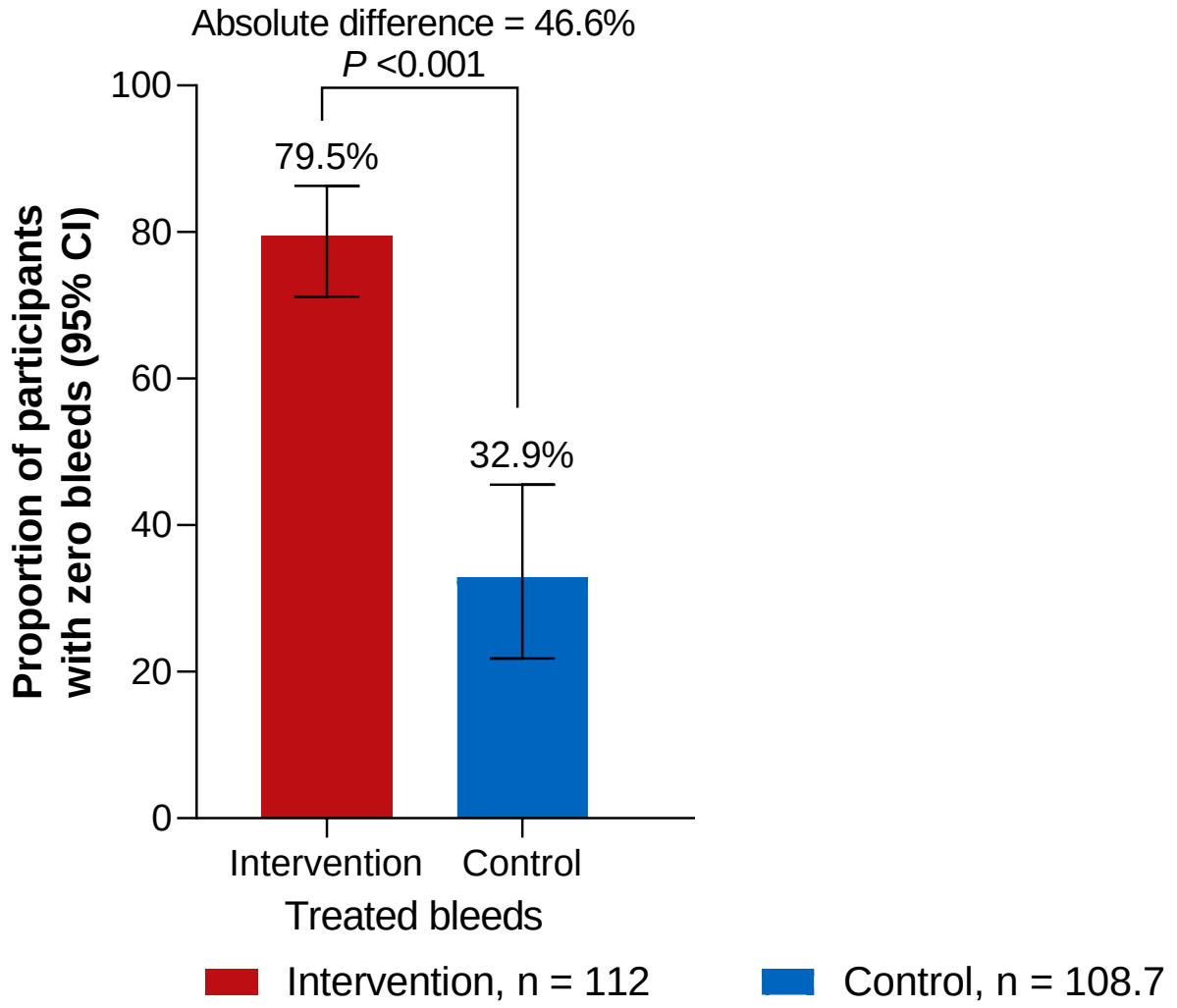
- Mean treated and all bleeds ABR were significantly lower
- Absolute differences of
  - Treated bleeds: –3.6 (0.8 vs 4.4), *P* <0.001
  - All bleeds: –3.6 (1.4 vs 5.0), *P* <0.001



ABR, annualized bleeding rate; CI, confidence interval.

Results: Proportion of participants with zero bleeds

- The proportions of participants with zero treated and all bleeds were significantly higher
  - Treated bleeds: 79.5% vs 32.9%, *P* <0.001
  - All bleeds: 52.7% vs 28.5%, *P* = 0.003



CI, confidence interval.

Conclusions

- The use of propensity scores produced cohorts balanced on important observable patient characteristics
- Participants receiving valoctocogene roxaparvovec demonstrated lower ABRs and higher proportions of participants with zero bleeds compared with participants receiving prophylactic FVIII
- Results of the propensity score analysis were consistent with GENEr8-1 findings[1]
  - Absolute difference in mean treated ABR: –4.1 (GENEr8-1) and –3.6 (PS analysis)
  - Absolute difference in proportion with zero treated bleeds: 48% (GENEr8-1) and 47% (PS analysis)
- The main limitation of the work is that propensity scoring uses *observable* patient characteristics
  - Sensitivity and scenario analyses are ongoing to ensure the results are robust

ABR, annualized bleeding rate; FVIII, factor VIII; PS, propensity score.

1) Ozelo et al. *N Engl J Med*. 2022;386(11):1013–25.

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Q&A