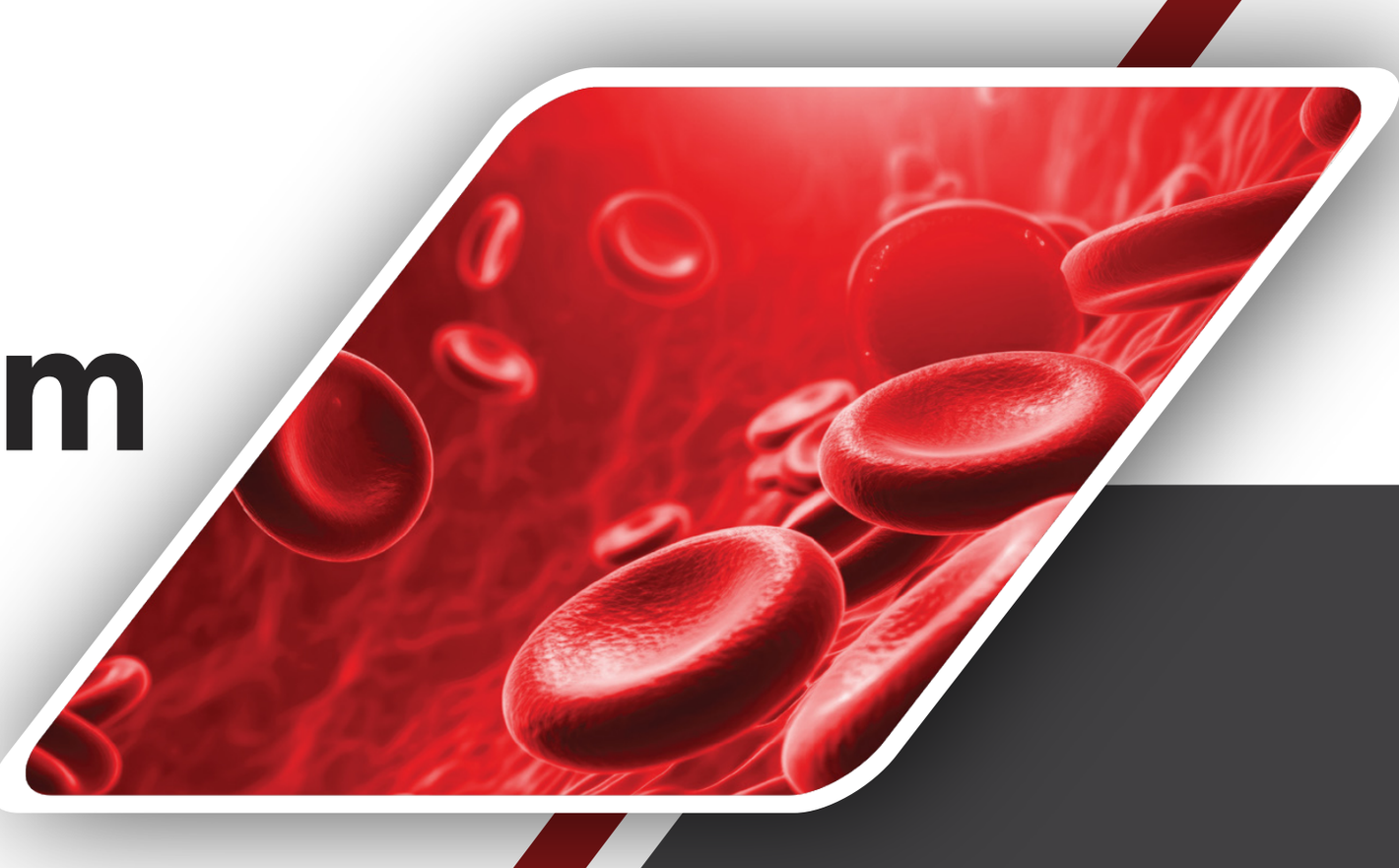


Achieving Freedom From Bleeding:

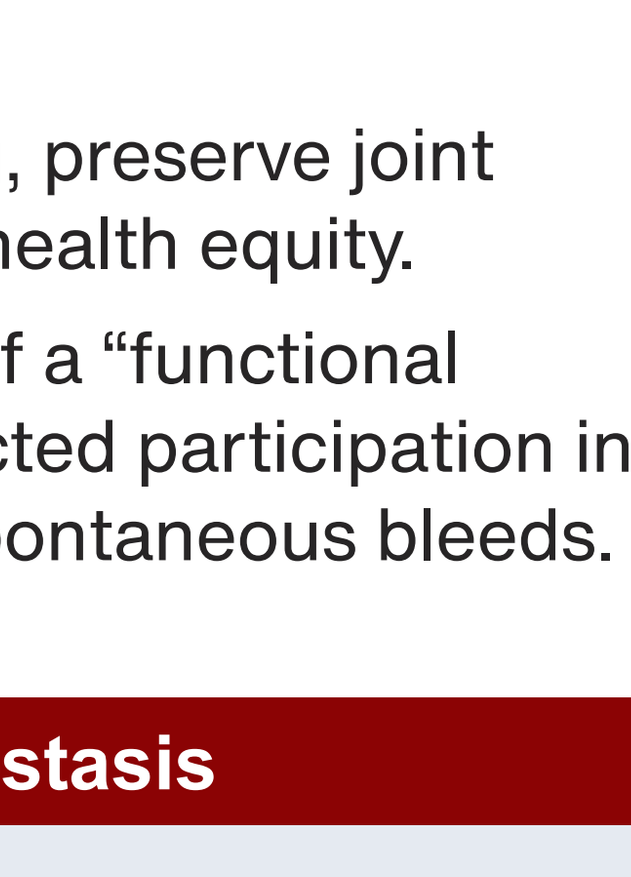
Exploring the Evolving Evidence on New and Emerging Treatment Strategies to Maintain Higher FVIII Levels

Baseline FVIII levels dictate the number of joint bleeds that will occur:

Low FVIII Levels → Joint Bleeds →
- Joint damage
- Hemophilic arthropathy
- Chronic pain
- Impaired HRQOL

- Prophylaxis in hemophilia aims to prevent joint damage, which arises from joint bleeds.
- All patients with severe hemophilia should be receiving prophylaxis that is sufficient to prevent joint bleeds at all times.

- **Around half of people with hemophilia** live with **chronic pain**.
- **More than half of patients report receiving pain management** from their healthcare provider, with around **40% reporting their pain is not well treated**.



There is a new therapeutic goal for hemophilia A: *health equity*.

- Normalized FVIII levels can prevent spontaneous bleeding, preserve joint function, and promote active living, which contributes to health equity.
- People with hemophilia can progress toward attainment of a "functional cure" by achieving specific milestones, including unrestricted participation in work and family life, normal mobility, and freedom from spontaneous bleeds.

Model of Milestones Toward Normal Hemostasis

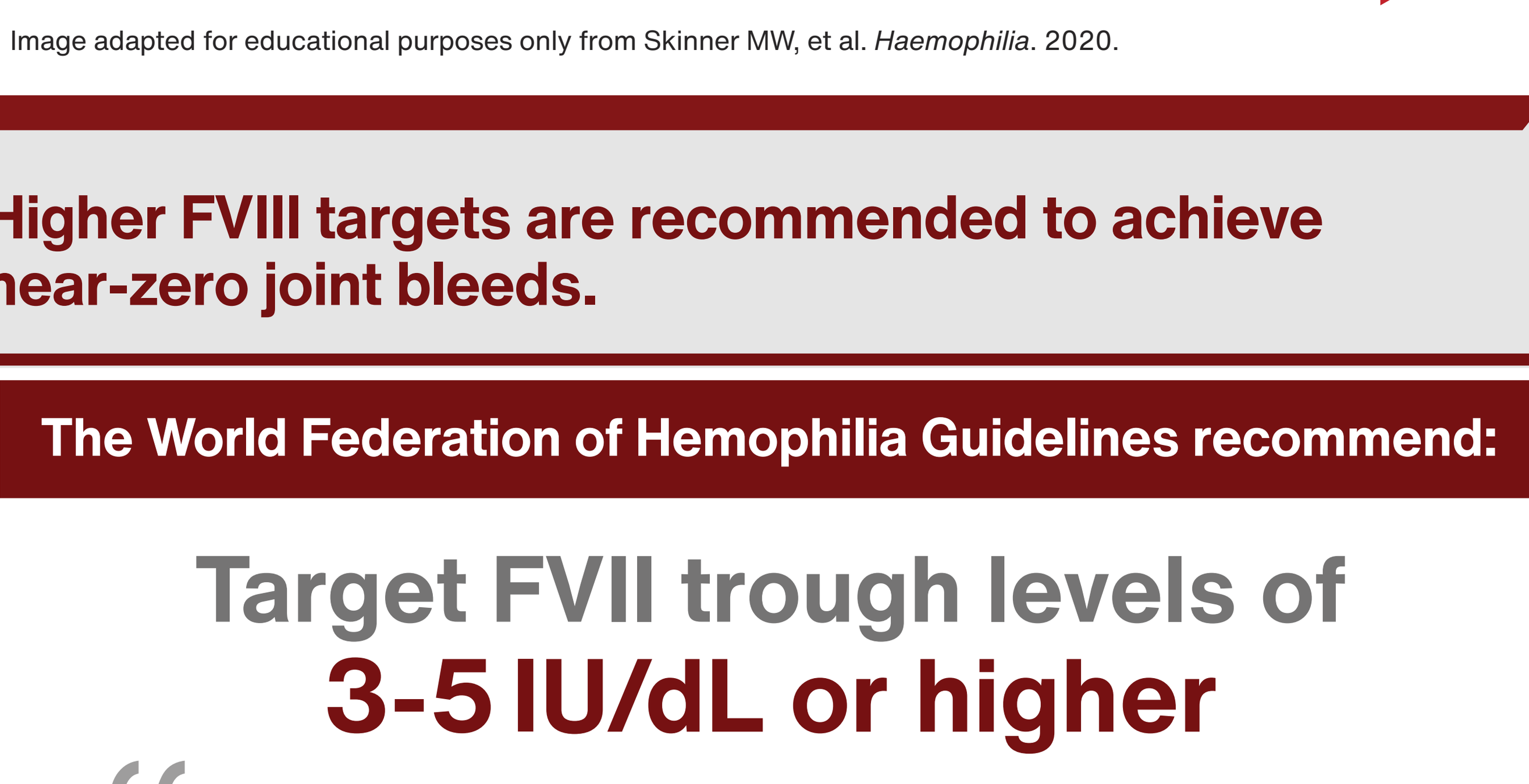


Image adapted for educational purposes only from Skinner MW, et al. *Haemophilia*. 2020.

Higher FVIII targets are recommended to achieve near-zero joint bleeds.

The World Federation of Hemophilia Guidelines recommend:

Target FVII trough levels of 3-5 IU/dL or higher

> *"Now recognizing that with a 1% trough level, patients remain at risk of bleeding, most clinicians would prefer to target higher trough levels (>3%-5%)."*
>
> — WFH Guidelines, 2020

Higher FVIII levels are associated with lower bleed rates:

A higher proportion of patients experience zero total and spontaneous bleeds when prophylaxis targets FVIII trough levels of 8%-12% compared to targeting levels of 1%-3%.

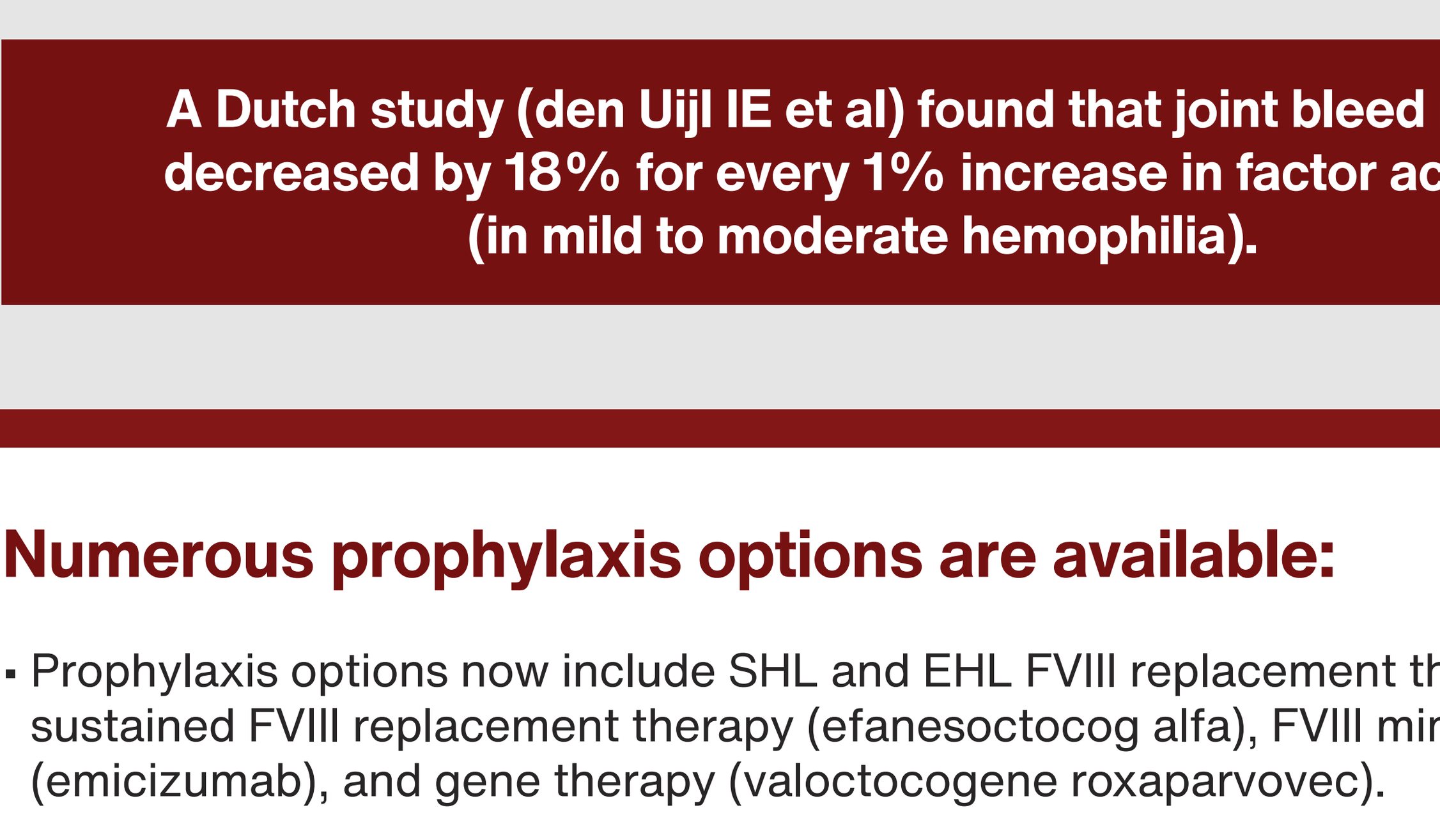


Image adapted for educational purposes from Klamroth R, et al. *Blood*. 2021.

A Dutch study (den Uijl IE et al) found that joint bleed rates decreased by 18% for every 1% increase in factor activity (in mild to moderate hemophilia).

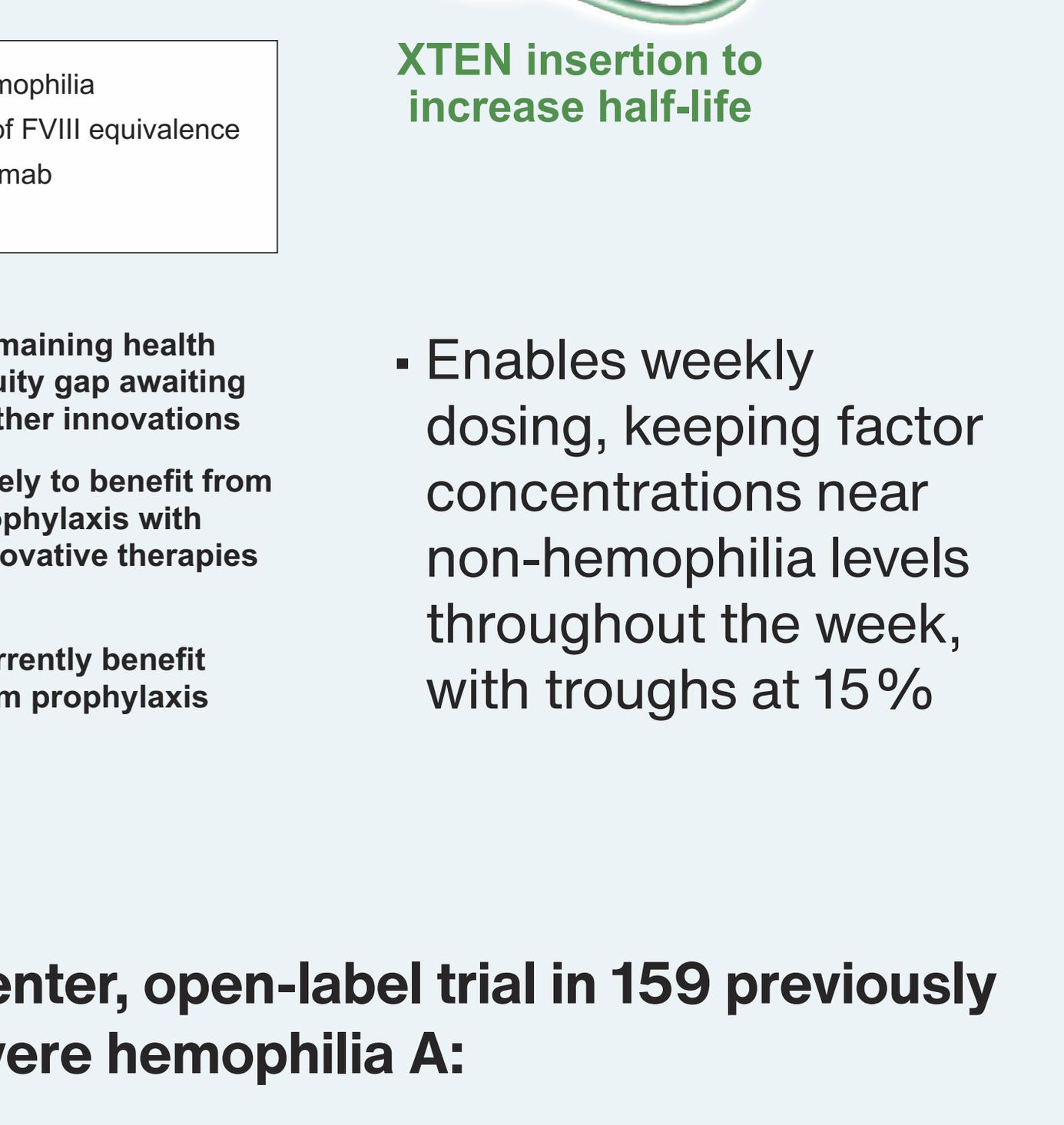
Numerous prophylaxis options are available:

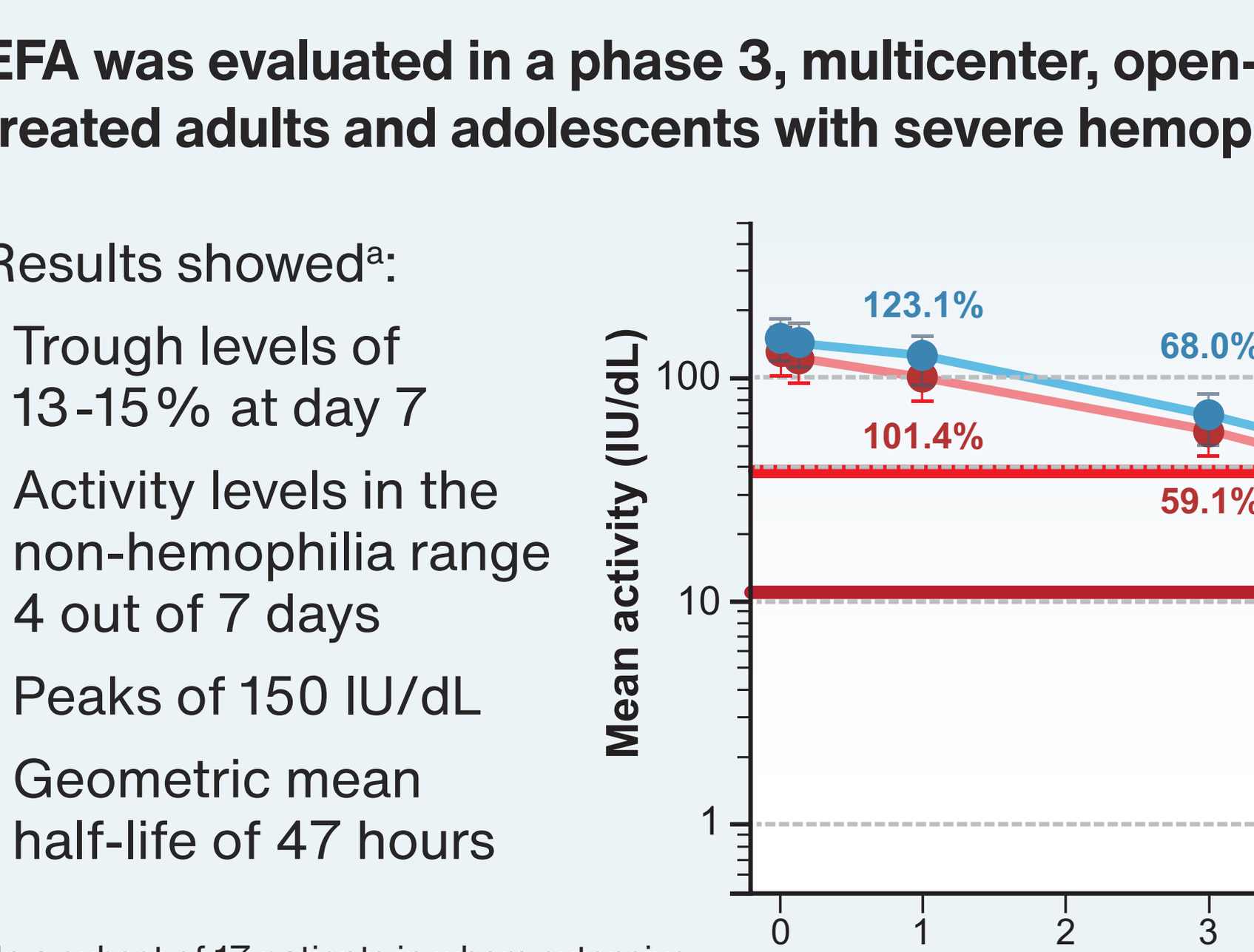
- Prophylaxis options now include SHL and EHL FVIII replacement therapy, high-sustained FVIII replacement therapy (efanesoctocog alfa), FVIII mimetic therapy (emicizumab), and gene therapy (valoctocogene roxaparvovec).
- **All forms of prophylaxis are superior to episodic therapy.**
- **Efanesoctocog alfa** and **valoctocogene roxaparvovec** achieve steady hemostasis without the peaks and troughs of factor replacement.

With such products available to patients, prophylaxis recommendations can now shift from what is feasible to what is optimal.

Efanesoctocog Alfa (EFA)

- Fusion protein comprising recombinant FVIII, a dimeric Fc, 2 XTEN polypeptides, and a VWF D'D3 domain
- Engineered to function independently of VWF, extending its half-life beyond typical limitations (~15-19 hours)

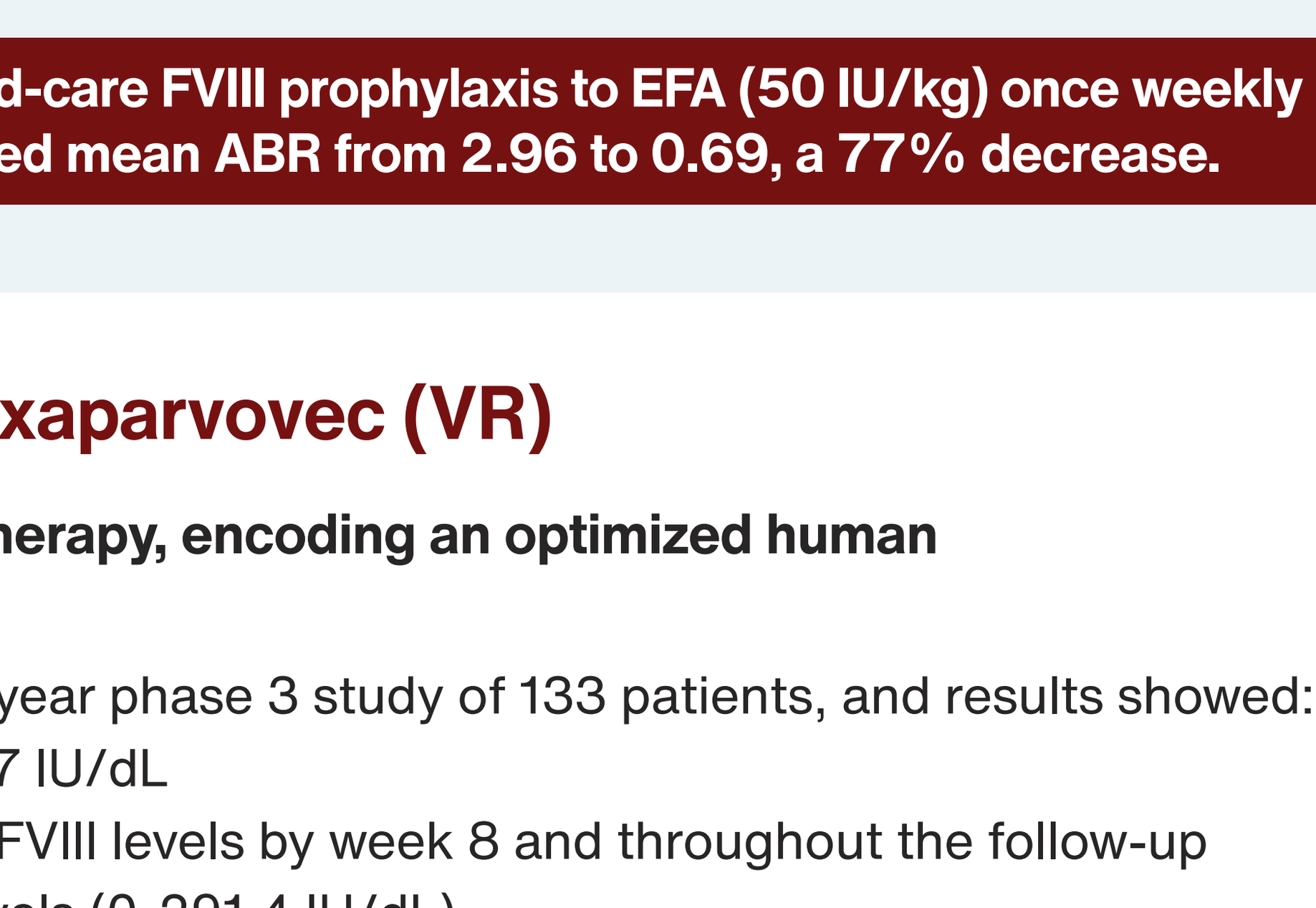




- Enables weekly dosing, keeping factor concentrations near non-hemophilia levels throughout the week, with troughs at 15%

EFA was evaluated in a phase 3, multicenter, open-label trial in 159 previously treated adults and adolescents with severe hemophilia A:

Results showed[a]:
- Trough levels of 13-15% at day 7
- Activity levels in the non-hemophilia range 4 out of 7 days
- Peaks of 150 IU/dL
- Geometric mean half-life of 47 hours



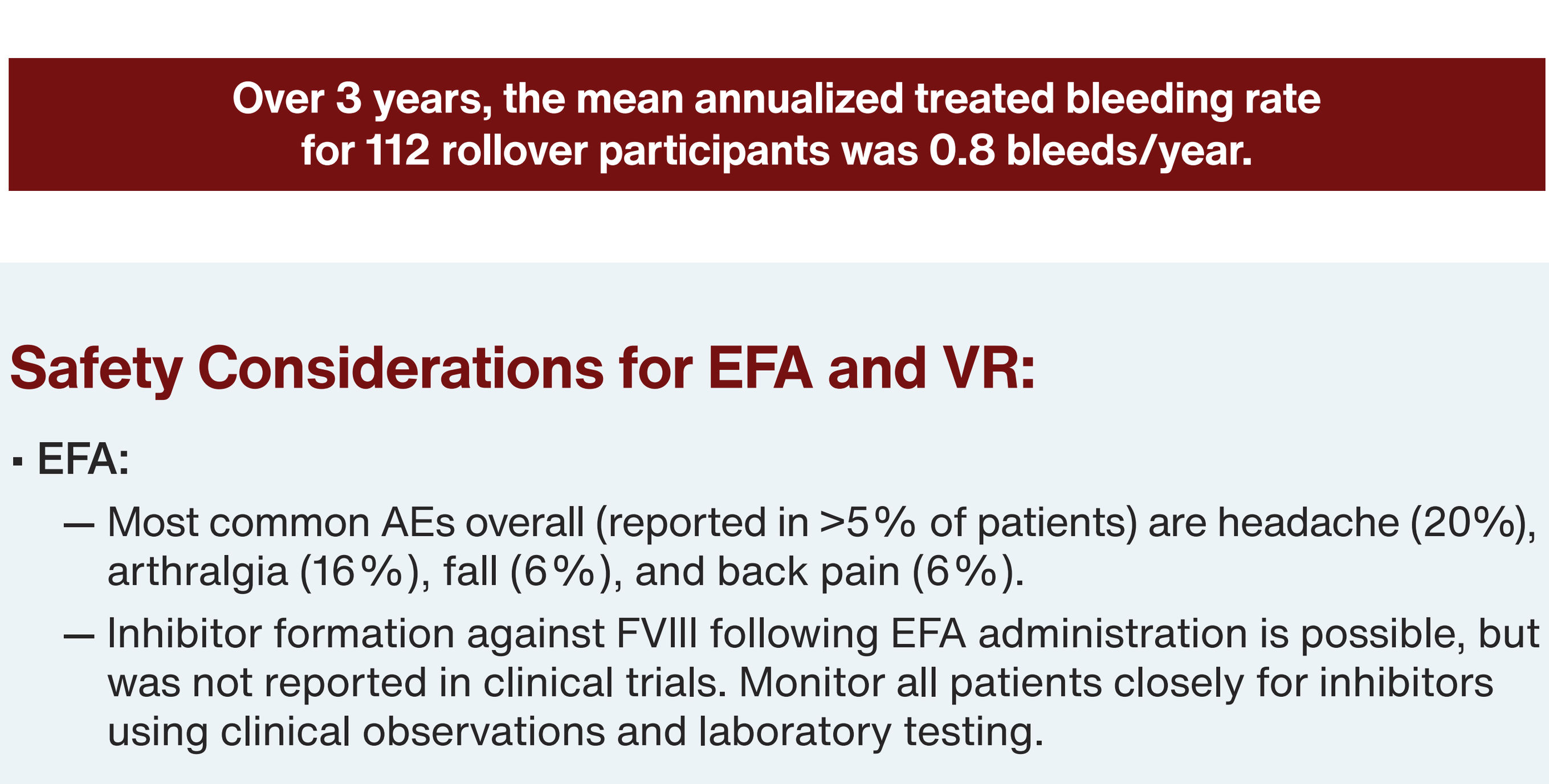
[a] In a subset of 17 patients in whom extensive pharmacokinetic analysis was done.

Switching from standard-care FVIII prophylaxis to EFA (50 IU/kg) once weekly for 52 weeks reduced mean ABR from 2.96 to 0.69, a 77% decrease.

Valoctocogene roxaparvovec (VR)

AAV5-mediated gene therapy, encoding an optimized human B domain-deleted FVIII

VR was evaluated in a 3-year phase 3 study of 133 patients, and results showed:
- Mean FVIII levels of 29.7 IU/dL
- Consistent therapeutic FVIII levels by week 8 and throughout the follow-up
- A wide range of FVIII levels (0-291.4 IU/dL)

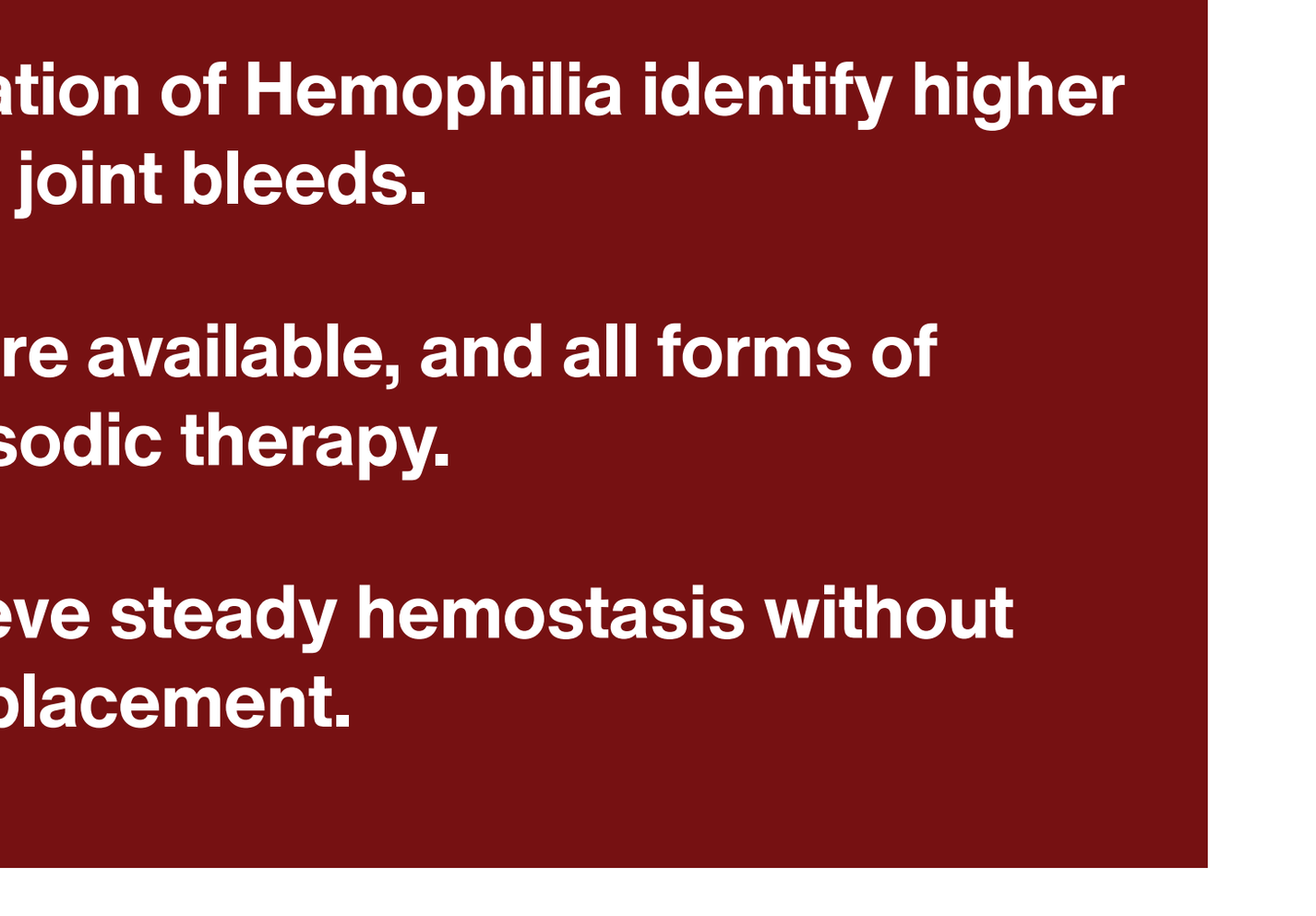


Over 3 years, the mean annualized treated bleeding rate for 112 rollover participants was 0.8 bleeds/year.

Safety Considerations for EFA and VR:

- EFA:
  - Most common AEs overall (reported in >5% of patients) are headache (20%), arthralgia (16%), fall (6%), and back pain (6%).
  - Inhibitor formation against FVIII following EFA administration is possible, but was not reported in clinical trials. Monitor all patients closely for inhibitors using clinical observations and laboratory testing.
- For VR, ALT increases were observed during clinical trials:
  - Typically occur within the first 3 months (in 86% of those receiving VR).
  - Presumed to be an immune response to the viral vector parts and can lead to expression loss.
  - Monitor ALT weekly for at least the first 6 months, and institute corticosteroid treatment in response to ALT elevations as recommended.
  - Monitor FVIII activity levels, as ALT elevation may be accompanied by a decrease in FVIII activity.

Summary



- **Baseline FVIII levels dictate the number of joint bleeds that will occur. Joint bleeds lead to joint damage, which impairs HRQOL.**
- **There is a new therapeutic goal for hemophilia A: *health equity*. People with hemophilia A can now progress toward a functional cure.**
- **Guidelines from the World Federation of Hemophilia identify higher FVIII targets to achieve near-zero joint bleeds.**
- **Numerous prophylactic options are available, and all forms of prophylaxis are preferable to episodic therapy.**
- **Newer agents (EFA and VR) achieve steady hemostasis without the peaks and troughs of FVIII replacement.**

Abbreviations

AA5: adeno-associated virus type 5
ABR: annualized bleeding rate
AE: adverse event
ALT: alanine aminotransferase
EHL: extended half-life
EFA: efanesoctocog alfa
FVIII: factor VIII
HRQOL: health-related quality of life
mITT: modified intention-to-treat
SHL: standard half-life
VR: valoctocogene roxaparvovec
VWF: von Willebrand factor

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