Segment 2: Guidelines for FVIII Levels

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The Roles of Factor Levels in Hemophilia Care

Diagnosis

- Diagnosis of hemophilia
- Evaluation of disease severity
- Detection of inhibitors

Clinical Management

- Dose adjustment of factor replacement therapies
- Monitoring during bleed management and surgery
- Optimizing factor dosing for PK-guided prophylaxis

PK, pharmacokinetic

1. Bowyer AE, et al. *Semin Thromb Hemost.* 2022;49(6):609-620. 2. Iorio A. *Hematology Am Soc Hematol Educ Program.* 2017;2017(1):595-604.

Modeling Approaches to Predict Optimal FVIII Trough Levels

FVIII Activity Levels Associated With Zero Joint Bleeds

Chowdary *et al.* 2020[1]

*Using pharmacokinetic models designed to estimate the FVIII levels linked to **zero** spontaneous bleeding episodes in people with severe hemophilia A receiving prophylaxis*

35%

Soucie *et al.* 2018[2]

Based on a regression model to predict joint bleeds in people with hemophilia A

30%

den Uijl *et al.* 2011[3]

Based on a multivariate model to estimate joint bleeds in people with hemophilia A

15%

1. Chowdary P, et al. *Thromb Haemost.* 2020;120(5):728-736. 2. Soucie J, et al. *Blood Adv.* 2018;2(16):2136-2144. 3. den Uijl I, et al. *Haemophilia.* 2011;17(1):41-44.

3

PROPEL Phase 3 Trial: Higher Trough Levels Improve Clinical Outcomes

OBJECTIVE	POPULATION	DESIGN
Compare efficacy of two FVIII trough level targets in individualized prophylaxis	People with hemophilia A on prophylaxis treatment	Randomized to target trough: 1–3% (standard) vs 8–12% (higher)

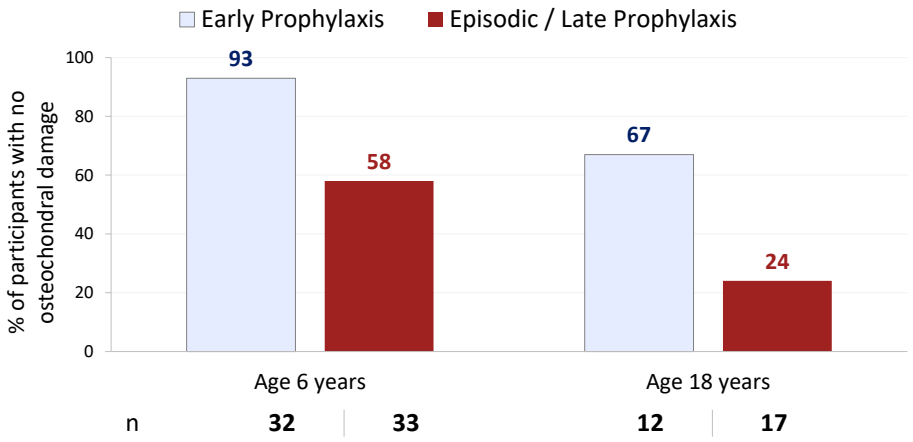
RESULTS	Trough 1–3%	Trough 8–12%
Zero total bleeds	42%	62%
Zero spontaneous bleeds	60%	76%
Zero spontaneous joint bleeds	65%	85%

TAKEAWAY: Higher trough levels reinforce the value of a personalized approach considering phenotype, PK profile, and bleed risk

PK, pharmacokinetic
Klamroth R et al. *Blood.* 2021;137(13):1818-1827.

Joint Outcome Study – Continuation

Percentage of children with no osteochondral damage at JOS completion (age 6 years), JOS-C completion (age 18 years)



Warren BB, et al. *Blood.* 2018;132(Supplement 1):382.

Subclinical Bleeds Produce Long-Term Clinical Impacts

Key findings from two landmark clinical studies on factor replacement therapy outcomes

US Joint Outcome Study

- MRI abnormalities were found in joints that have never had overt bleeding
- Early initiation of prophylaxis is protective vs delayed initiation
  - Insufficient to completely prevent damage
- Standard prophylaxis does not fully protect joints through adolescence in severe hemophilia A

Canadian Dose Escalation Study

- Soft tissue changes detected in index joints without clinically reported bleeding
- Hemosiderin detected in many of these "bleed-free" joints

31%
Index joints with soft tissue changes

26%
"Bleed-free" joints with hemosiderin

Standard prophylaxis regimens leave room for improvement in joint protection

1. Warren BB, et al. *Blood Adv.* 2020;4(11):2451-2459. 2. Kraft J, et al. *J Thromb Haemost.* 2012;10(12):2494-2502.

Half-Life Extension in FVIII: Approaching — and Breaking — the VWF Ceiling

VWF binding limits half-life of conventional EHL FVIII; decoupling enables further extension

Conventional EHL FVIII (Fc fusion, PEGylation)	**Efanesoctocog alfa**
• Primarily stabilized in plasma by binding to **von Willebrand factor (VWF)**	• **Decouples FVIII from VWF**
• Subject to a **VWF-imposed half-life ceiling**	• Half-life **~3–4×** standard half-life
• Half-life improved only **~1.5–2×** standard half-life	• Half-life is **independent of VWF**
• Typical prophylaxis: **~2× / week** infusions	• Once-weekly dosing maintained FVIII in non-hemophilia range (> 40%) for up to 4 days in pivotal trial

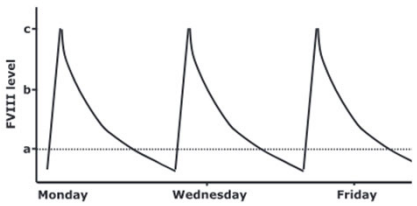
Note: Half-life values reflect different studies, populations, and assays — direct head-to-head comparisons are limited.

1. Konkle BA, et al. *N Engl J Med*. 2020;383(11):1018-1027. 2. von Drygalski A, et al. *N Engl J Med*. 2023;388(4):310-318.
3. Lissitchkov T, et al. *Res Pract Thromb Haemost*. 2023;7(4):100176. EHL, extended half-life; FVIII, factor VIII; SHL, standard half-life; VWF, von Willebrand factor.

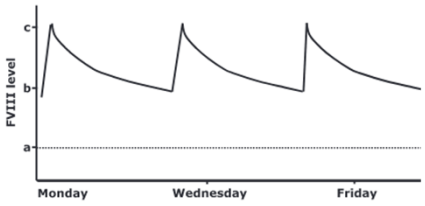
Clinical Impact of Extended Half-Life Prophylaxis

Tailor prophylaxis to each patient's clinical status, lifestyle, needs, and preferences

Standard Half-Life (SHL)



Extended Half-Life (EHL)



Decreased number of infusions

Sustained higher trough levels

Improved adherence and burden

Favorable clinical, safety and QoL outcomes

1. Hermans C, et al. *Crit Rev Oncol Hematol.* 2022;174:103678. 2. Mahdi AJ, et al. *Br J Haematol.* 2015;169(6):768-776.