Nordic Coagulation Meeting 2023

A simulation study to provide guidance for individuals transitioning from emicizumab to valoctocogene roxaparvovec

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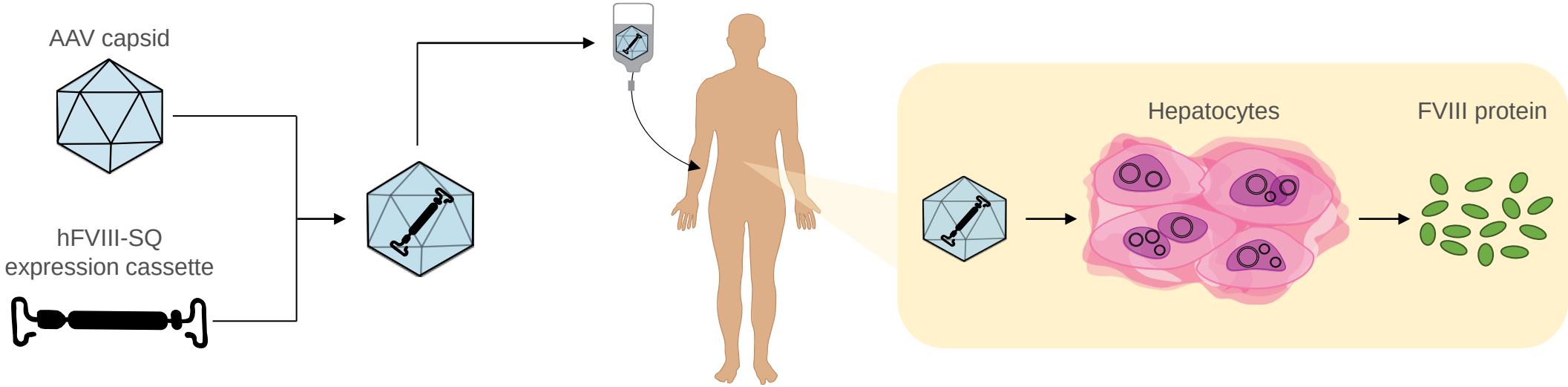
Disclosures

- Simon Harris is an employee and stockholder of BioMarin Pharmaceutical Inc.

Valoctocogene roxaparvovec for severe hemophilia A

- Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) transfers a FVIII coding sequence that enables endogenous FVIII production in people with severe hemophilia A (FVIII ≤1 IU/dL)[1,2]
- Valoctocogene roxaparvovec was evaluated in a phase 3, single-arm, open-label study (GENEr8-1) in 134 participants treated with a single infusion[1,2]
  - Most individuals reached therapeutic FVIII activity levels ≥5 IU/dL within 4 to 12 weeks



AAV, adeno-associated virus; FVIII, factor VIII; hFVIII-SQ, human FVIII, SQ variant.

1. Ozelo M, et al. *N Engl J Med*. 2022;386(11):1013-25. 2. Mahlangu J, et al. *N Engl J Med*. 2023;388(8):694-705.

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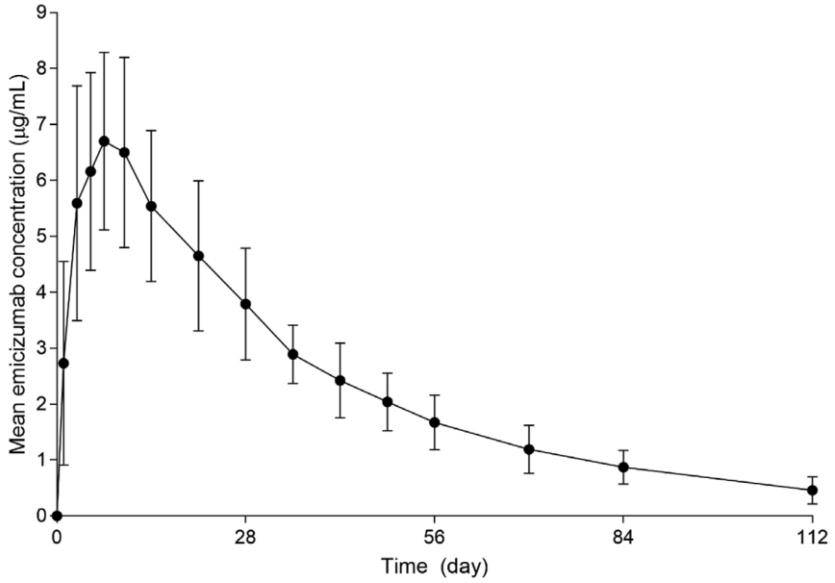
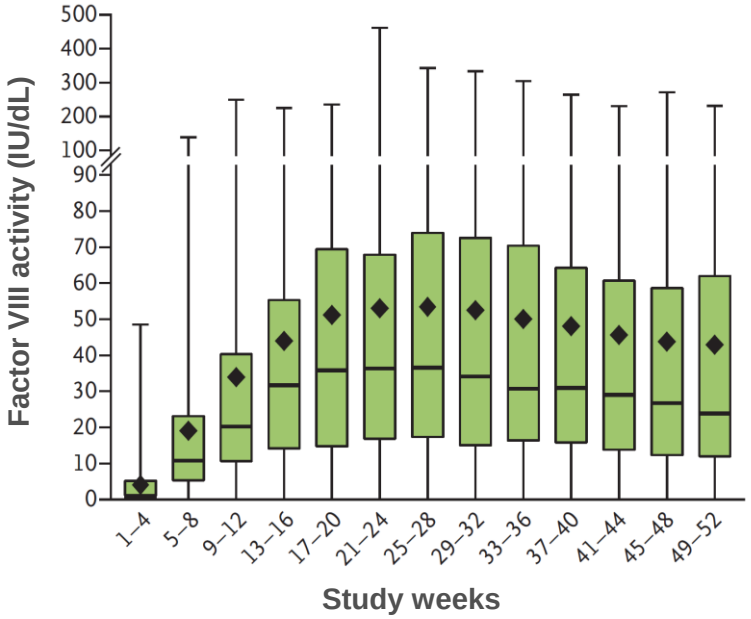
Study objective

- We used pharmacokinetic simulations to provide guidance on the timing for discontinuation of emicizumab in individuals transitioning to valoctocogene roxaparvovec
  - During GENEr8-1 enrollment, emicizumab was an investigational product and its use was excluded

Emicizumab is a long-acting SHA treatment[1]



Valoctocogene roxaparovovec is an SHA treatment with slow onset[2]



Data are presented as the mean ± SD.
SD, standard deviation; SHA, severe hemophilia A.
1. Li H, et al. *Clin Pharmacol Drug Dev*. 2021;10(1):30-8. 2. Ozelo M, et al. *N Engl J Med*. 2022;386(11):1013-25.

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Assumptions for estimation of bleeding risk categories

FVIII activity levels (IU/dL)	Average emicizumab levels at each week (µg/mL)	Bleeding risk category[a]
<5	<15	Greater than emicizumab
	15 to <100	Same as emicizumab
	≥100	Less than emicizumab
5 to <15	<65	Same as emicizumab
	≥65	Less than emicizumab
≥15	Any	Less than emicizumab

[a]Bleeding risk was defined by the emicizumab exposure-response relationship.[1] If emicizumab concentrations fell below 15 µg/mL and FVIII activity levels were less than 5 IU/dL, then individuals were assumed to have a greater bleeding risk.[1,2,3,4] FVIII activity levels >15 IU/dL were assumed to provide hemostatic efficacy.

FVIII, factor VIII.

1. Shima M, et al. *N Engl J Med*. 2016;374(21):2044-53. 2. Lehtinen P, et al. *Haemophilia*. 2022;28(2):53-5. 3. Tang A, et al. *Res Pract Thromb Haemost*. 2021;5(Suppl 2). 4. Jonsson F, et al. *Clin Pharmacokinet*. 2021;60(7):931-41.

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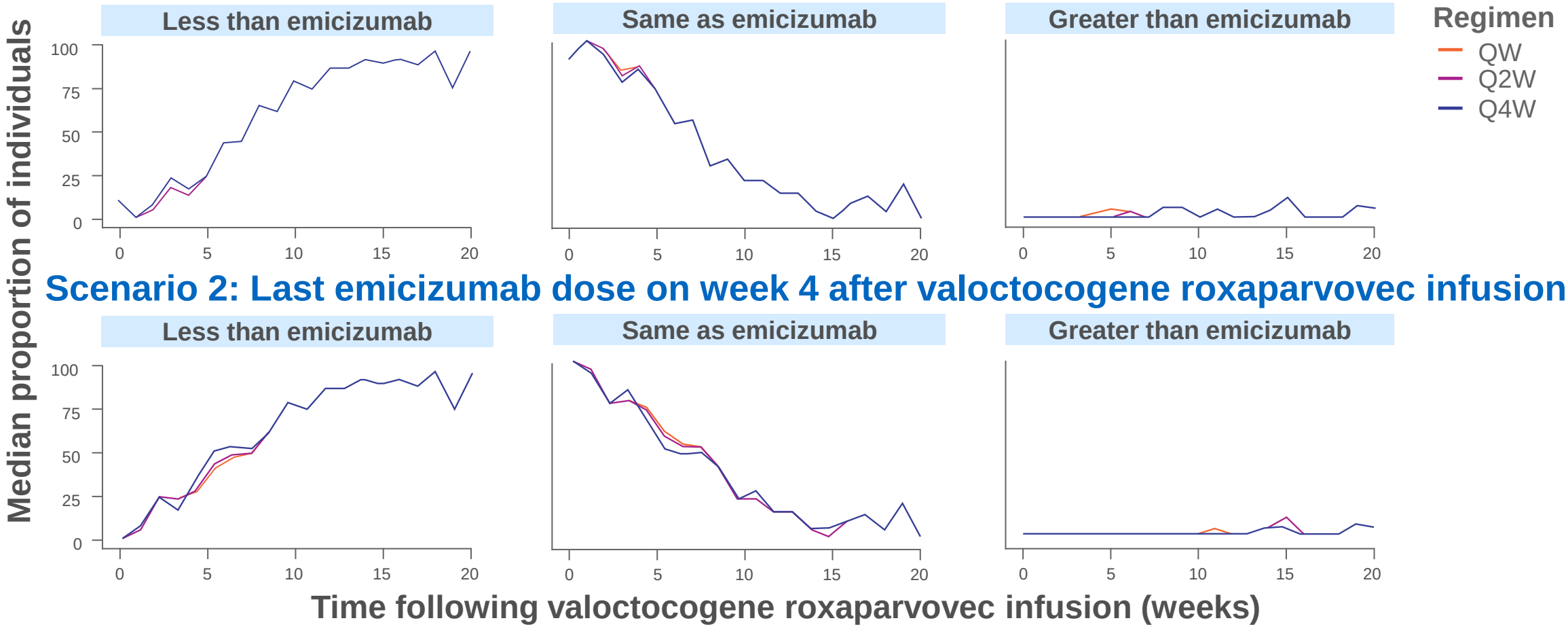
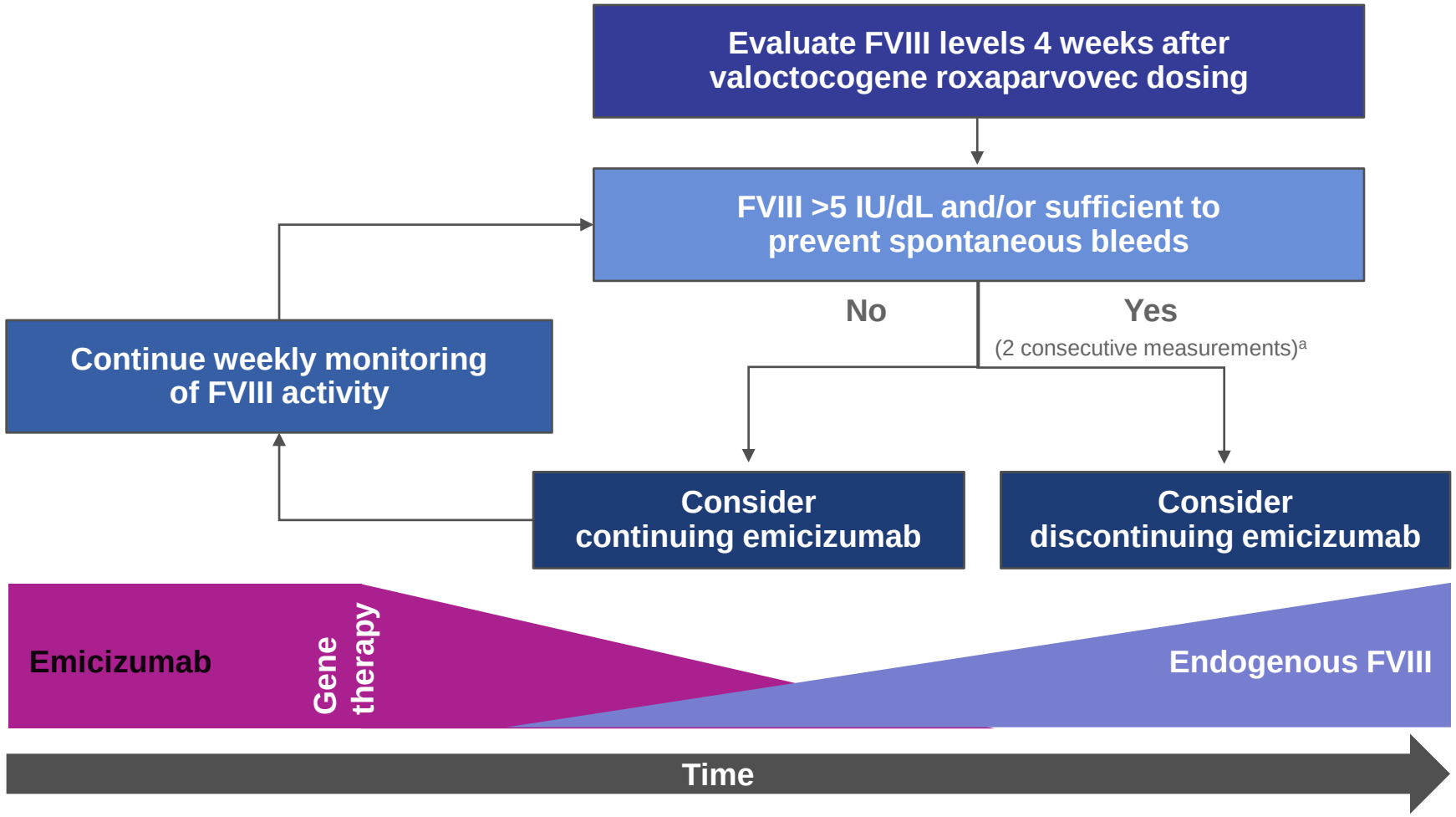
Proportion of individuals with bleeding risk over time

Scenario 1: Last emicizumab dose on same day as valoctocogene roxaparvovec infusion



Q2W, once every 2 weeks; Q4W, once every 4 weeks; QW, once weekly.

Timing for discontinuation of emicizumab after gene therapy



[a]Prescribers should consider continuing emicizumab prophylaxis and continue weekly monitoring of FVIII activity levels until 2 consecutive weekly measurements ≥5 IU/dL are achieved before discontinuation of emicizumab.
FVIII, factor VIII.

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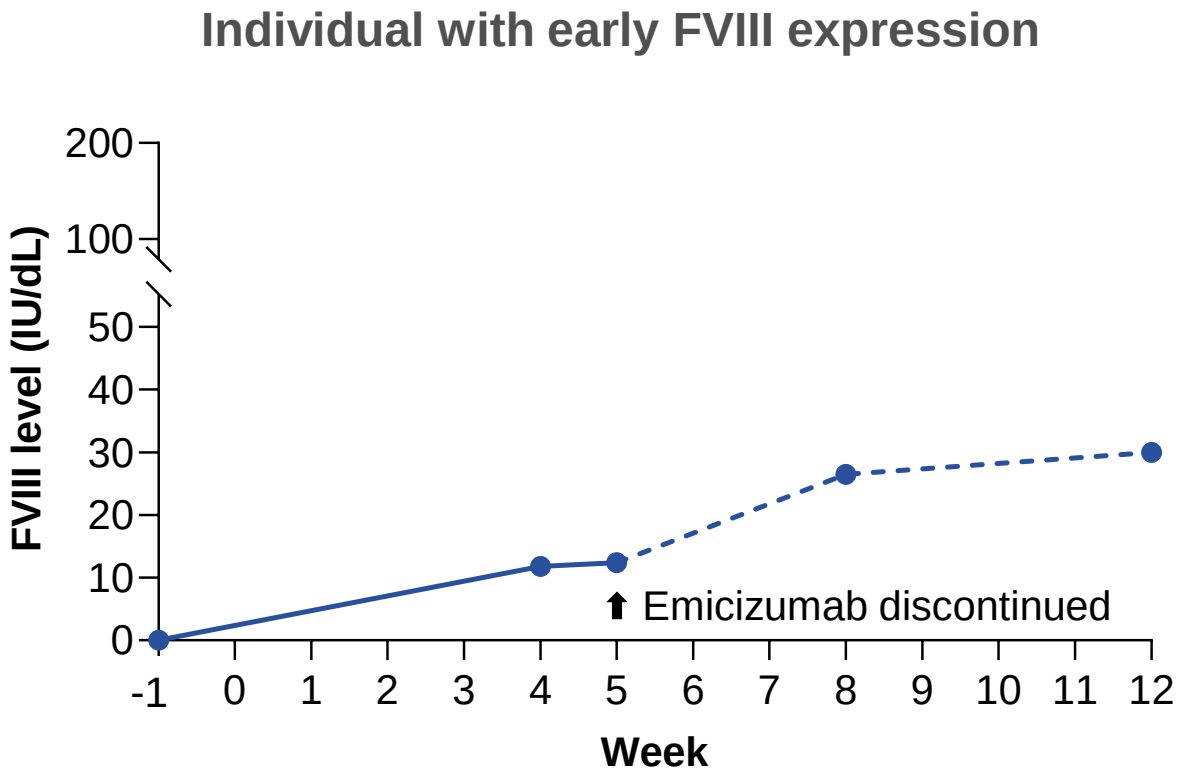
Theoretical case example

(1 of 5)

- A 37-year-old male had early FVIII levels >5 IU/dL for 2 consecutive weeks
  - He discontinued emicizumab at week 5
- Twelve weeks after infusion, his FVIII levels continued to rise >30 IU/dL, and he remains bleed free



Valoctocogene roxaparvovec infusion occurred at week 0. The blue line denoting FVIII activity level begins at the last dose of emicizumab administration before valoctocogene roxaparvovec infusion, with the solid portion of the line denoting when individuals received emicizumab prophylaxis. The dashed portion of the blue line denotes the period after discontinuation of emicizumab prophylaxis. FVIII activity level was measured with the CSA using bovine reagents.
CSA, chromogenic substrate assay; FVIII, factor VIII.

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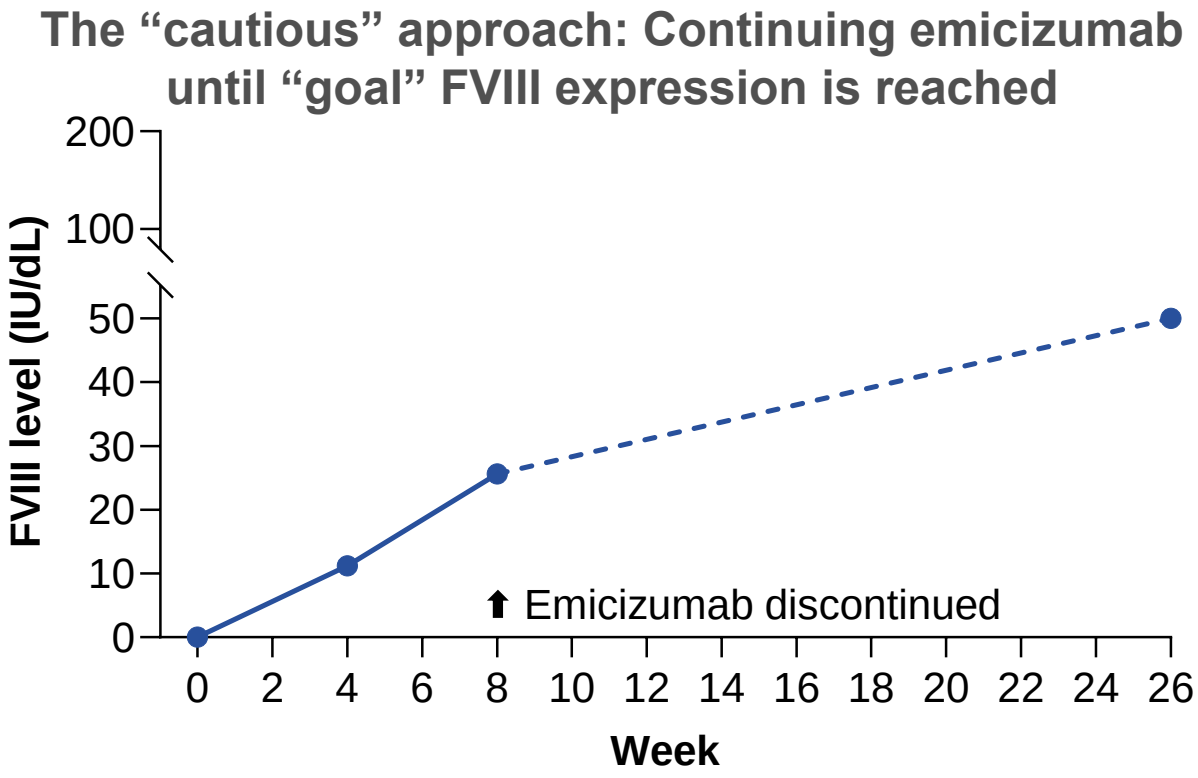
Theoretical case example

(2 of 5)

- An active 45-year-old male had a FVIII level of 11.2 IU/dL at week 4 and 1 traumatic bleed from exercise
- He reached FVIII levels >20 IU/dL but was concerned about discontinuing emicizumab because of his active lifestyle
- He agreed to stop emicizumab after being reminded the hemostatic efficacy of emicizumab is ~10 to 15 IU/dL
- At week 26, the individual's FVIII level remained >50 IU/dL, and he did not have any additional spontaneous bleeds



FVIII activity level was measured with the CSA using bovine reagents.
CSA, chromogenic substrate assay; FVIII, factor VIII.

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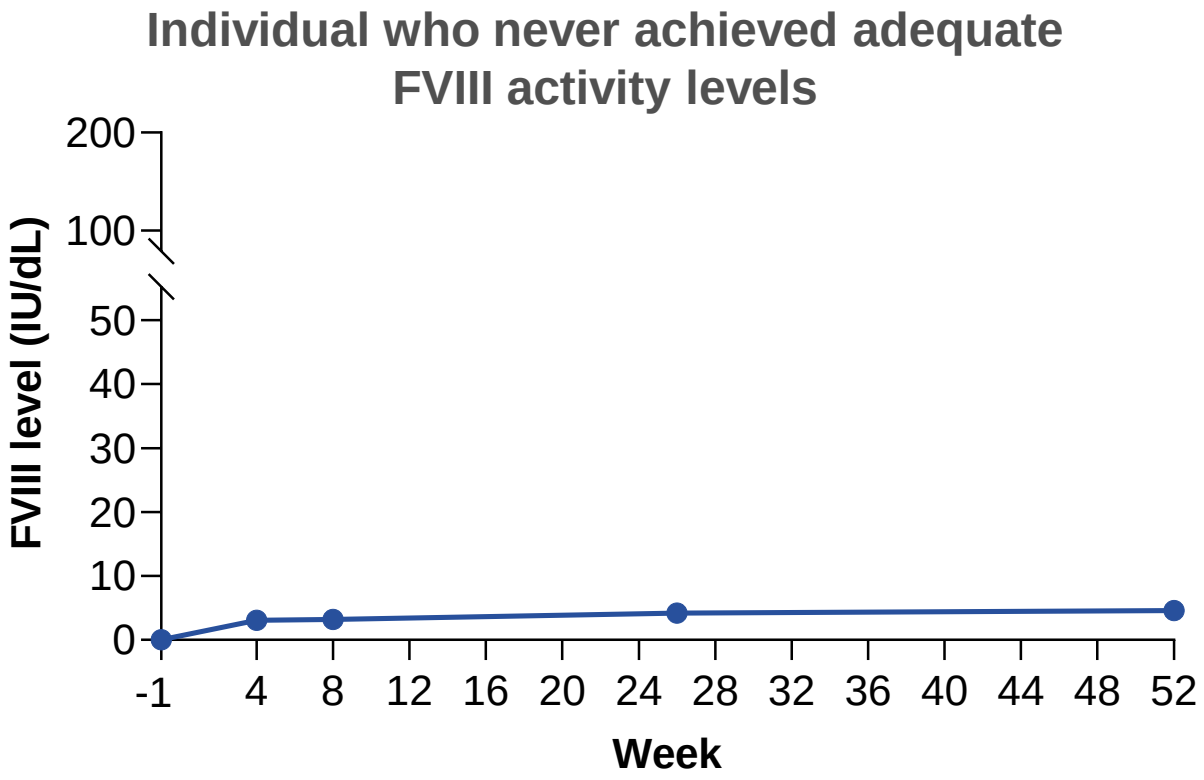
Theoretical case example

(3 of 5)

- A 53-year-old male's FVIII level was 3.1 IU/dL at week 4
- In weeks 8 to 26, his FVIII level remained between 3 and 4.8 IU/dL
- He remained on emicizumab for routine prophylaxis due to consistently low FVIII expression after gene therapy
- One year later, the individual remains generally well, and his FVIII level at week 52 was 4.6 IU/dL



FVIII activity level was measured with the CSA using bovine reagents.
CSA, chromogenic substrate assay; FVIII, factor VIII; W, week.

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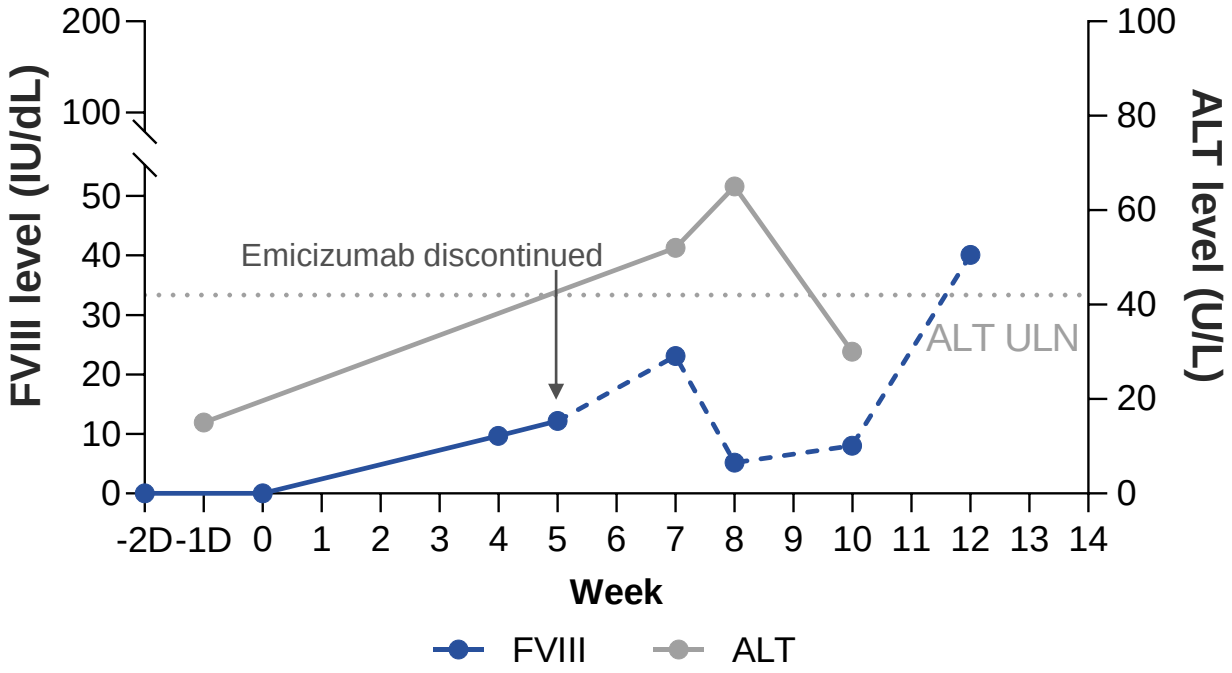
Theoretical case example

(4 of 5)

- A 26-year-old male's FVIII level gradually increased, and he discontinued emicizumab
- At week 7, his ALT increased to 52 U/L
- The next week, his ALT remained elevated, and his FVIII activity level declined
  - Prednisone 60 mg was initiated
- ALT levels returned to normal, and his FVIII levels began to rise again
- By week 12, his FVIII level was 40.1 IU/dL and he remained off emicizumab

Individual whose FVIII levels were adequate by week 4 but declined after transaminitis



The ALT ULN was 42 U/L. FVIII activity level was measured with the CSA using bovine reagents.
ALT, alanine transaminase; CSA, chromogenic substrate assay; D, day; FVIII, factor VIII; ULN, upper limit of normal.

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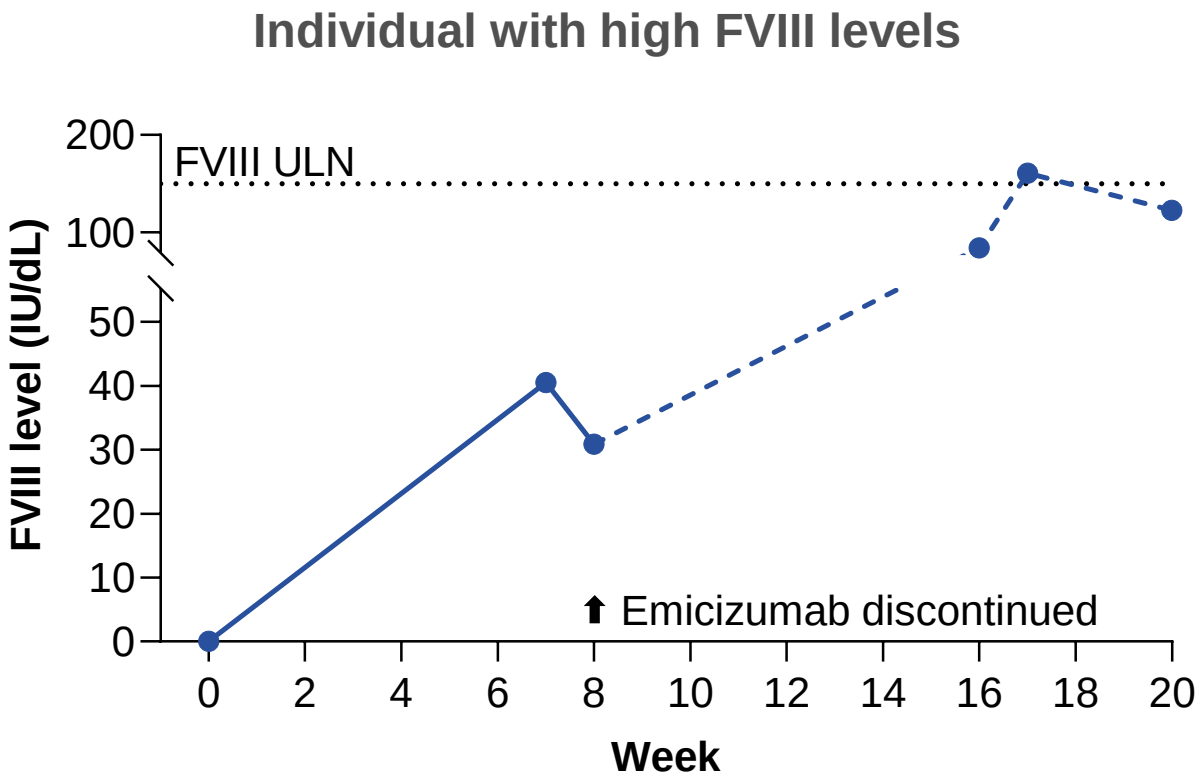
Theoretical case example

(5 of 5)

- A 33-year-old male's FVIII level was 40.5 IU/dL at week 7
  - He discontinued emicizumab the following week
- FVIII levels continued to rise and at week 17 it was >ULN at 161 IU/dL
  - His ALT levels remained normal
- There were no risk factors for TE events and thus no anticoagulation or antiplatelet therapy was administered
- His FVIII level returned to normal ranges, and no AEs were reported



The FVIII ULN was 150 IU/dL. FVIII activity level was measured with the CSA using bovine reagents.
AE, adverse event; ALT, alanine transaminase; CSA, chromogenic substrate assay; FVIII, factor VIII; TE, thromboembolic; ULN, upper limit of normal.

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Conclusions

- Pharmacokinetic simulations showed no meaningful difference in the risk of bleeding while transitioning to valoctocogene roxaparvovec treatment following different emicizumab discontinuation times and dosing regimens
- The bleeding risk is determined by the dynamic balance of decaying emicizumab levels and increasing gene therapy–derived endogenous FVIII
- These original data suggest individuals on emicizumab prophylaxis can safely transition to valoctocogene roxaparvovec using multiple approaches

FVIII, factor VIII

Acknowledgments

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Questions?