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

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Background

- Severe hemophilia A (SHA) is an X-linked recessive bleeding disorder defined by a factor VIII (FVIII) activity level <1 IU/dL[1]
- Emicizumab is an antibody mimicking the function of FVIII used for routine prophylaxis in SHA to prevent bleeding[2]
- Valoctocogene roxaparvovec is a gene therapy for SHA that uses an adeno-associated virus serotype 5 (AAV5) vector to transfer a B-domain–deleted human FVIII-coding sequence that provides improved protection from bleeds compared with FVIII prophylaxis[1]
  - Valoctocogene roxaparvovec was evaluated in a phase 3, single-arm, open-label study (NCT03370913; GENEr8-1) in 134 participants with SHA who were treated with a single infusion[1]
  - Most individuals reached therapeutic FVIII activity levels ≥5 IU/dL within 4 to 12 weeks
- At the time of GENEr8-1 initiation, emicizumab was an investigational product, and individuals using it were excluded.[1] Thus, there are limited data available regarding how long to continue emicizumab prophylaxis after receiving valoctocogene roxaparvovec to maintain hemostasis

Aim

- To use pharmacokinetic simulations of emicizumab, paired with the FVIII kinetics observed in GENEr8-1, to provide guidance on timing for discontinuation of emicizumab in individuals transitioning from emicizumab prophylaxis to valoctocogene roxaparvovec gene therapy while maintaining hemostatic control

Methods

Emicizumab pharmacokinetic simulations

- A population pharmacokinetic model was published previously that evaluated the pharmacokinetics of emicizumab using a database that included 389 participants with hemophilia A from the HAVEN 1, 2, 3, and 4 clinical trials[3]
  - Three emicizumab dosing regimens were evaluated: 3 mg/kg once weekly (QW) for 4 weeks, as a loading dose, followed by 1.5 mg/kg QW; 3 mg/kg once every 2 weeks (Q2W); and 6 mg/kg once every 4 weeks (Q4W)[3]
  - The mean trough concentration for all 3 dosing regimens is approximately 40 µg/mL[3] and hypothesized to correspond with a similar level of hemostatic control as FVIII activity of 10 to 15 IU/dL[4]
- The published model was used to simulate the in vivo, steady-state, emicizumab concentrations presented here. Briefly, 500 replicates of simulated emicizumab concentration–time profiles for 134 participants of GENEr8-1 were conducted for 3 emicizumab dosing regimens (QW, Q2W, and Q4W)

Bleeding risk estimation

- Simulated in vivo emicizumab concentrations were merged with FVIII activity time-course data for each of the 134 participants of GENEr8-1 to calculate the risk of bleeding at weekly intervals for up to 20 weeks after valoctocogene roxaparvovec infusion
- Bleeding risk was based on the assumptions outlined in **Table 1**

Table 1. Assumptions for the estimation of bleeding risk categories

FVIII activity levels (IU/dL)	Average emicizumab levels at each week (µg/mL)	Bleeding risk category
<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

Bleeding risk was defined by the emicizumab exposure-response relationship.[4] 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.4,5,6,7 FVIII activity levels >15 IU/dL were assumed to provide hemostatic efficacy. FVIII, factor VIII.

Two scenarios with different timing for discontinuation of emicizumab

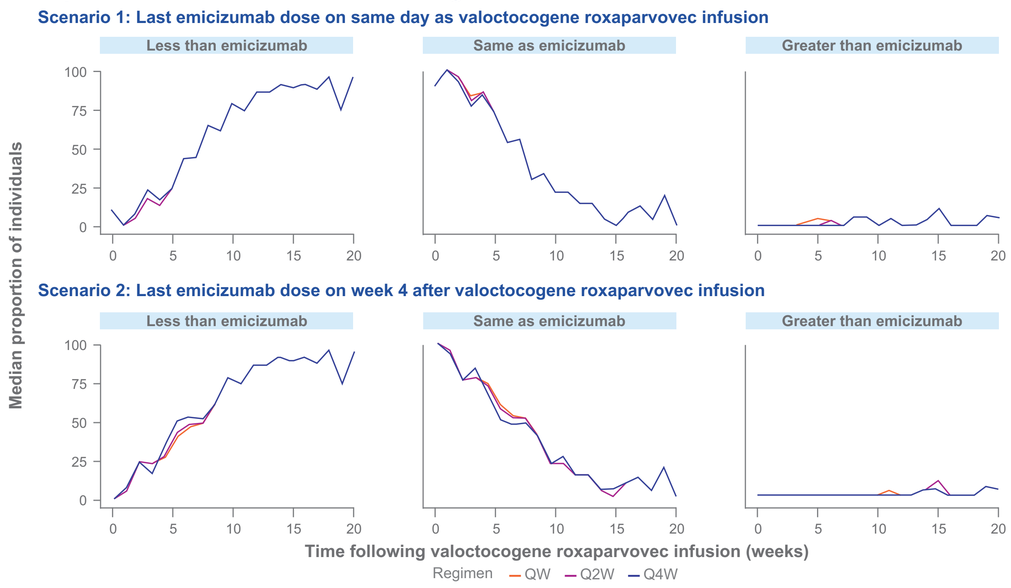
- Two transition scenarios were evaluated for individuals transitioning from emicizumab to valoctocogene roxaparvovec
  - Scenario 1: Last dose of emicizumab on the day of valoctocogene roxaparvovec infusion
  - Scenario 2: Last dose of emicizumab occurred 4 weeks after valoctocogene roxaparvovec infusion
- For either transition scenario, emicizumab levels would have declined by greater than 90% by the end of the presented modeling experiments

Results

Estimation of bleeding risk

- Early discontinuation of emicizumab with the last dose on the day of valoctocogene roxaparvovec infusion (scenario 1) vs additional doses of emicizumab for up to 4 weeks (scenario 2) offered similar levels of hemostatic control **(Figure 1)**
  - Bleeding risk was also comparable across the 3 emicizumab dosing regimens for both scenarios

Figure 1. Proportion of individuals with bleeding risk over time

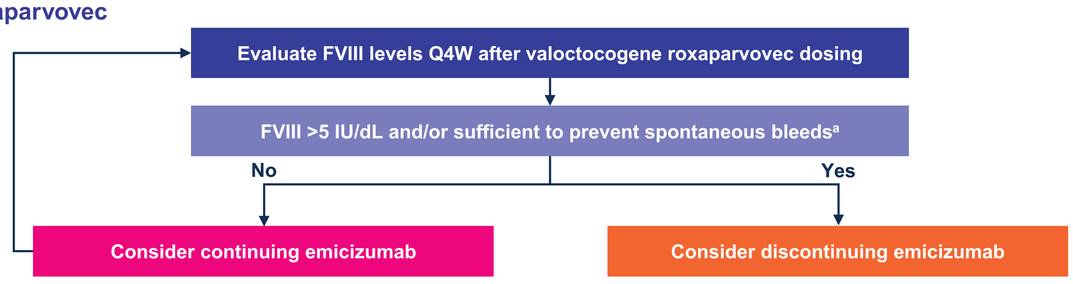


FVIII, factor VIII; Q2W, once every 2 weeks; Q4W, once every 4 weeks; QW, once weekly.

Timing of discontinuation of emicizumab after gene therapy

- An algorithm to guide decisions around when emicizumab can be discontinued was developed based on the results of the simulations to estimate bleeding risk **(Figure 2)**
- The chromogenic substrate assay (CSA) using bovine reagents must be used to monitor endogenous FVIII activity in those receiving emicizumab
  - The interaction between emicizumab and human factor IXa and factor X yields artificially high results[8]

Figure 2. Treatment algorithm for discontinuation of emicizumab when transitioning to valoctocogene roxaparvovec

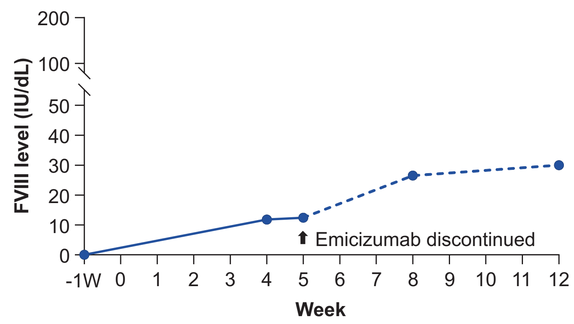


[a]Prescribers should consider continuing emicizumab prophylaxis and continue weekly monitoring of FVIII activity levels until 2 consecutive weekly measurements ≥5 IU/dL are achieved before discontinuation of emicizumab. FVIII, factor VIII; Q4W, once every 4 weeks.

Theoretical case examples

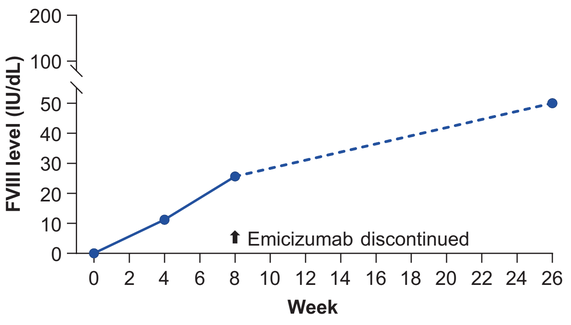
- To highlight specific considerations that could arise with individuals who are transitioning from emicizumab to valoctocogene roxaparvovec, several theoretical case examples are presented based on actual responses from GENEr8-1 study participants
  - All individuals had SHA and no history of inhibitors. FVIII activity was measured weekly with the CSA using bovine reagents

Individual with early FVIII expression by week 4



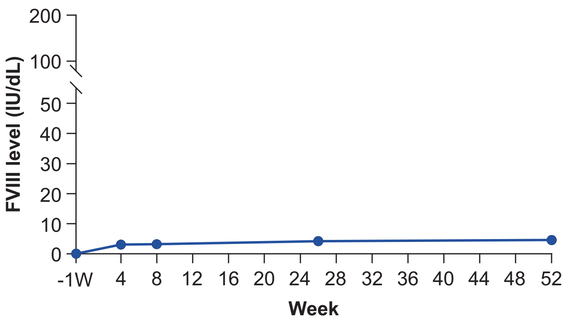
- A 37-year-old male continued emicizumab 1.5 mg/kg QW for routine prophylaxis after valoctocogene roxaparvovec infusion
- At weeks 4 and 5, his FVIII activity level was 11.8 IU/dL and 12.4 IU/dL, respectively
- Due to FVIII activity levels >5 IU/dL for 2 consecutive weeks, he discontinued emicizumab at week 5
- Twelve weeks after infusion, his FVIII activity levels continued to rise >30 IU/dL, and he remains bleed free

The "cautious" approach to continue emicizumab until "goal" FVIII expression was reached



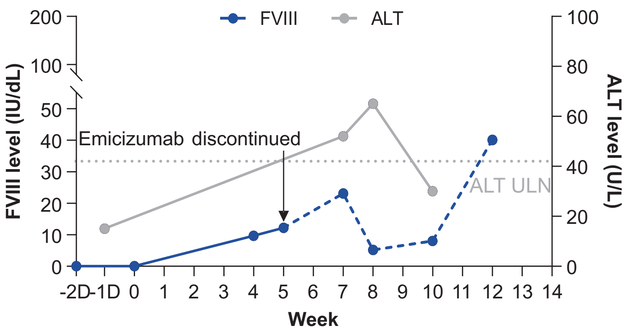
- A 45-year-old male continued emicizumab 1.5 mg/kg QW for routine prophylaxis after valoctocogene roxaparvovec infusion
- At week 4, his FVIII activity level was 11.2 IU/dL and he had 1 traumatic bleed from exercise that was treated with recombinant FVIII. He continued prophylaxis with emicizumab due to his risk of bleeding from regular exercise
- By week 9, he had FVIII activity levels >20 IU/dL for 2 consecutive weeks. However, with his history of bleeds, the individual and his hematologist were cautious about discontinuing emicizumab
- They were reminded that hemostatic efficacy from emicizumab is roughly equivalent to 10 to 15 IU/dL, less than his current FVIII activity level. They agreed to stop emicizumab and continued weekly monitoring of FVIII activity levels
- At week 26, the individual's FVIII activity remained >50 IU/dL, and he did not have any additional spontaneous bleeds

Individual who never achieved adequate FVIII activity levels by 12 weeks post dosing



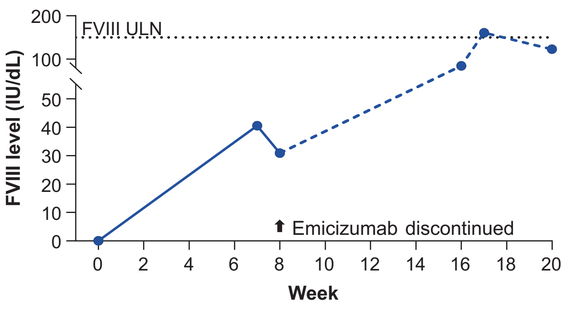
- A 53-year-old male continued emicizumab 3 mg/kg Q2W for routine prophylaxis after valoctocogene roxaparvovec infusion
- At week 4, his FVIII activity level was 3.1 IU/dL, and he continued his prophylaxis with emicizumab since his FVIII activity level was still <5 IU/dL
- In weeks 8 through 26, his FVIII activity level remained between 3 and 4.8 IU/dL
- He remained on emicizumab 405 mg Q2W for routine prophylaxis due to consistently low FVIII expression after gene therapy
- One year later, this individual remains generally well, and his FVIII activity level at week 52 was 4.6 IU/dL

Individual with FVIII activity levels that appeared adequate by weeks 4 to 8 but declined after transaminitis



- A 26-year-old male continued emicizumab 1.5 mg/kg QW for routine prophylaxis after valoctocogene roxaparvovec infusion
- At weeks 4 and 5, his FVIII activity levels were 9.7 IU/dL and 12.2 IU/dL, respectively, and so he discontinued emicizumab
- At week 7, FVIII activity continued to rise but his alanine aminotransferase (ALT) increased to 52 U/L, which was greater than 2 times his ALT prior to valoctocogene roxaparvovec infusion
- During his week 8 assessment, his ALT remained elevated, and his FVIII activity level declined. Prednisone 60 mg was initiated. Subsequently, ALT levels returned to normal, and his FVIII activity levels began to rise again
- At week 12, his FVIII activity was 40.1 IU/dL. He continued to remain off emicizumab for prophylaxis due to continued hemostatic control after valoctocogene roxaparvovec infusion

Individual with high FVIII levels



- A 33-year-old male continued his regular schedule of emicizumab 6 mg/kg Q4W after valoctocogene roxaparvovec infusion
- At week 7, his FVIII activity level was 40.5 IU/dL, and he discontinued emicizumab the following week
- His FVIII activity level continued to rise and at week 17 it was greater than the upper limit of normal (ULN) at 161 IU/dL. His ALT levels remained normal
- Based on his hematologist's assessment, there were no risk factors for thromboembolic events and thus no anticoagulation or antiplatelet therapy was administered. Within 3 weeks, his FVIII activity level returned to within normal ranges, and no adverse events were reported
- He has remained off emicizumab for prophylaxis due to continued hemostatic control after valoctocogene roxaparvovec infusion

Discussion

- 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

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Disclosures

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