same day as infusion, and second, given 4 weeks after valoctocogene roxaparvovec. **Results:** Discontinuation of emicizumab the day of valoctocogene roxaparvovec infusion compared with continued dosing for 4 weeks offered similar levels of hemostatic control. The time course for bleeding risk was comparable across the emicizumab dosing regimens for both scenarios. An algorithm to provide guidance for discontinuing emicizumab was developed based on these results. To guide how treatment decisions for emicizumab discontinuation may vary among individuals, theoretical case examples were developed based on participants of GENEr8-1. **Conclusions:** Regardless of the emicizumab dose or dosing regimen, pharmacokinetic simulations showed no meaningful difference in the risk of bleeding related to FVIII and FVIII equivalent activity 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. COIs for presenting author. Suresh Agarwal is an employee and stockholder of BioMarin Pharmaceutical Inc.

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QUANTITATIVE PHARMACOKINETIC MODEL TO CHARACTERIZE AND EXTRAPOLATE LONG-TERM FVIII ACTIVITY LEVELS IN PATIENTS WITH SEVERE HEMOPHILIA A TREATED WITH VALACTOCOGENE ROXAPARVOVEC

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Aim: Valoctocogene roxaparvovec delivers a B-domain deleted factor VIII (FVIII) coding sequence with an adeno-associated virus vector to reduce bleeding and FVIII concentrate use in people with severe hemophilia A. This study aimed to characterize the long-term trajectory of transgene-derived FVIII activity using a linear mixed effects (LME) model to estimate mean and median FVIII activity levels 5 years post-infusion. **Methods:** In GENEr8-1, an open-label, single-arm, multicenter phase 3 trial, 134 participants with severe hemophilia A received a single 6 x 10^{13} vg/kg dose of valoctocogene roxaparvovec. FVIII activity was assessed using the chromogenic substrate assay and one-stage assay. A previously published quantitative pharmacokinetic (PK) modelwas updated to extrapolate FVIII activity levels to 5 years post-infusion. Ln-transformed FVIII activity values from week 76 to 104 were fit to the LME model with random effects for participants on slope and intercept using a restricted maximum likelihood method with the lmer package in the R statistical computing software (R Foundation for Statistical Computing, Vienna, Austria). The precision of parameter estimates and model diagnostics were evaluated to confirm goodness-of-fit. The model and extrapolation approach was further qualified by comparing to observed FVIII activity at week 156. **Results:** The final LME model dataset included 928 observations from 120 participants. The long-term trajectory of FVIII activity was consistent with first-order elimination kinetics starting at week 76. Model parameter estimates were consistent with the previously published model; diagnostic plots showed no major deficiencies. FVIII activity was extrapolated to 5 years post-gene transfer. Mean and median FVIII activity extrapolations at week 156 were consistent with observed values, confirming adequacy of the model. **Conclusions:** Pharmacokinetic modeling indicates valoctocogene roxaparvovec-derived FVIII activity levels will remain in the mild hemophilia range for ≥5 years post-gene transfer for the majority of patients treated. **COIs for presenting author: Suresh Agarwal** is a paid employee of BioMarin Pharmaceutical Inc. and holds stock ownership with BioMarin Pharmaceutical Inc.

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BLEEDING, FVIII ACTIVITY, AND SAFETY 3 YEARS AFTER GENE TRANSFER WITH VALOCTOCOGENE ROXAPARVOVEC: RESULTS FROM GENER8-1

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