Supplementary Material

Methodology

Predictive Modeling Methods
Penalized logistic regression builds on a classical logistic regression approach by incorporating a penalty on the regression coefficients, which helps to alleviate overfitting; in particular, the L2 (ridge) penalty was implemented. The extent of influence of the penalty was a hyperparameter that was tuned during the learning phase. Random forests have several properties that are well suited to this use-case and are also, in some cases, complementary to logistic regression. Specifically, random forest is an ensemble of decision trees that are sensitive to interactions and non-linear relationships between variables, as well as being robust to overfitting due to the combination of multiple decision trees on different subsamples of data in terms of patient observations and variables. Several hyperparameters can be tuned as part of the random forest algorithm, including the maximum depth of each decision tree and the minimum number of samples that must be present at each leaf node.

Model Validation Data Strategy
To validate model performance, it is generally preferred to use a subset of patients that are excluded from model learning (training set) and used exclusively for assessing the performance of the final model. Given the model sample size available here (in terms of unique patient counts), models were developed and evaluated using a nested cross-validation methodology, composed of eight inner folds and eight outer folds. The inner cross-validation was used to select optimal model hyperparameters via a grid search, which was then applied and evaluated in the outer cross-validation to measure performance on “unseen” data. Model performance was measured as the average performance across the outer test folds. To assess the stability of model performance, the average scores and confidence intervals were reported over 25 distinct runs of the nested cross-validation strategy. This combined approach of repeated nested cross-validation yields stable scores with minimal bias, while maximizing usage of the limited underlying dataset.
Supplementary Table S1 Clinically relevant variables used for the predictive analyses

| Variable types                  | Variable descriptions                                                                 | Model                                                        |
|---------------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------|
| Patient demographics            | Age (years)                                                                            | Pre-N8-GP prophylaxis and post-N8-GP prophylaxis             |
|                                 | Body mass index at baseline (kg/m²)                                                   |                                                              |
|                                 | Type of treatment regimen prior to trial (prophylaxis/on-demand)                       |                                                              |
|                                 | Height at baseline (m)                                                                 |                                                              |
|                                 | Historical annualized bleeding rate                                                   |                                                              |
|                                 | Body weight at baseline (kg)                                                          |                                                              |
| History analysis                | Frequency of dosing (interval in days)                                                |                                                              |
|                                 | FVIII product given (recombinant/plasma-derived)                                      |                                                              |
|                                 | Treated bleeds prior to prophylaxis (n)                                                |                                                              |
|                                 | Common doses used to treat a bleed (n)                                                 |                                                              |
|                                 | Dose for on-demand treatment (IU/kg)                                                   |                                                              |
|                                 | Time on previous regimen (months)                                                     |                                                              |
|                                 | Dose for prophylaxis (IU/kg)                                                          |                                                              |
|                                 | Mutation type [V1/V3] (mutation type)                                                 |                                                              |
|                                 | Underlying gene defect (known/unknown)                                                |                                                              |
|                                 | History of hemophilia A among relatives (true/false)                                   |                                                              |
|                                 | Number of inhibitor tests (n)                                                         |                                                              |
|                                 | Number of recovery tests (n)                                                          |                                                              |
| Laboratory results analysis     | Anti-PEG antibodies (titer)                                                           |                                                              |
|                                 | Screening binding anti N8-GP (% B/T)                                                   |                                                              |
|                                 | von Willebrand factor (IU/mL)                                                         |                                                              |
|                                 | Hepatitis C antibodies (present/absent)                                               |                                                              |
|                                 | Hemoglobin (g/L)                                                                      |                                                              |
|                                 | N8-GP binding antibodies (titer)                                                      |                                                              |
|                                 | Platelets (10⁹/L)                                                                     |                                                              |
| Physical examination analysis   | Musculoskeletal system [at V1 screening] (score: 1 = normal; 2 = abnormal, not clinically significant; 3 = abnormal, clinically significant) |                                                              |
|                                 | Skin [at V1 screening] (score: 1 = normal; 2 = abnormal, not clinically significant; 3 = abnormal, clinically significant) |                                                              |
| Vital signs analysis            | Diastolic blood pressure (mm Hg)                                                      |                                                              |
| Medical history                 | Body system or organ class grouped as:                                                 | Pre-N8-GP prophylaxis (Visit 2)⁴ and post-N8-GP prophylaxis   |
|                                 | • Musculoskeletal (n of events)                                                       |                                                              |
|                                 | • Surgical and medical procedures (n of events)                                       |                                                              |
| Pharmacokinetic                 | Mean FVIII trough level up until each model time point (IU/mL)                        |                                                              |
|                                 | Mean FVIII activity at 30 minutes up until each model time point (IU/mL)               |                                                              |
| Bleeds                          | Cumulative number of treated bleeds up until each model time point (n)                | Post-N8-GP prophylaxis                                       |

Abbreviations: FVIII, factor VIII; V, visit.

⁴The baseline and PK model included single measurements of trough level and FVIII activity at 30 minutes per patient.