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ORIGINAL ARTICLE

External qualification of the Web-Accessible Population Pharmacokinetic Service–Hemophilia (WAPPS-Hemo) models for octocog alfa using real patient data

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Abstract

Background: Existing adult patient pharmacokinetic (PK) data from the published Advate vs Kovaltry PK crossover study were used for this validation study. This data set is appropriate for qualification, given that it has not been previously submitted to Web-Accessible Population Pharmacokinetic Service–Hemophilia (WAPPS-Hemo) and will not have impacted the WAPPS-Hemo models for Kovaltry.

Objective: To compare the population PK parameters for Kovaltry (BAY 81-8973) derived from the WAPPS-Hemo models with PK parameters derived from noncompartmental analysis (NCA), using a validation PK dataset.

Methods: The qualification data set included Kovaltry factor activity (10 samples per infusion) and anthropometric data for 18 patients. Two analyses were performed comparison of Bayesian forecasting from the WAPPS-Hemo models versus NCA using the full 10-sample data set; and comparison of Bayesian forecasting using the full versus reduced 4- and 3-sample data sets. Agreement between outcomes was assessed by quantifying the variability and bias of the error.

Results: Comparison of WAPPS-Hemo models versus NCA led to well-correlated outcomes despite a systematic overprediction of clearance. Population PK models demonstrated greater consistency with NCA on one-stage data, compared with chromogenic data. WAPPS-Hemo model results were consistent in reduced sampling compared to full sampling. Inclusion of a 48-hour time point in the reduced sampling greatly improved the consistency with full sampling.

Discussion: Qualification of population PK models and their use for Bayesian forecasting in full and reduced sampling is an essential step toward their validation. The evaluations performed in this study support the confidence of PK parameter estimates provided by the models.

Essentials

- Population pharmacokinetic (popPK) models can estimate factor VIII (FVIII) PK using sparse FVIII measurements and patient characteristics.
- Octocog alfa PK from popPK was compared to noncompartmental analysis (NCA) validation data.
- PopPK models and NCA were well correlated despite a systematic overprediction of clearance.
- PopPK models were consistent in full and sparse sampling; a 48-hour sample improved consistency.

1 | INTRODUCTION

Prophylactic replacement of factor VIII (FVIII) is currently the gold standard treatment to prevent bleeding episodes in hemophilia A, as it effectively reduces arthropathy or joint damage in patients compared to on-demand treatment.[1,2] Time spent below a certain FVIII activity threshold is correlated to the risk of spontaneous bleeds in prophylaxis.[3] Consequently, trough FVIII activity or time spent below a critical FVIII activity are the outcomes most targeted in prophylaxis. However, these outcomes need to be derived from pharmacokinetic (PK) parameters that usually display wide variability among patients.[4]

The new ISTH recommendations[5] rely heavily on the use of population PK (popPK) models and associated Bayesian forecasting to derive individual PK estimates from only a few FVIII activity measurements plus patient characteristics. PopPK modeling aims at quantifying PK variability in a population and identifying which patient characteristics influence this variability and to what extent. The developed model is then used as prior information along with patient-specific information (eg, body weight, age, FVIII activity) to perform Bayesian forecasting, thus generating the individual PK. Once PK estimates for the patient are derived, they can be used to tailor dosing regimens that minimize the time spent below a desired FVIII threshold.[6]

The Web-Accessible Population Pharmacokinetic Service–Hemophilia (WAPPS-Hemo) platform is a web-based tool that uses such a popPK approach on a limited number of plasma FVIII activity samples to provide individual PK estimates to hemophilia treaters with the aim of tailoring the patient's prophylaxis regimen. The WAPPS-Hemo platform provides users with an estimate of an individual's PK parameters and FVIII activity at different time points. A clinical calculator is then accessible to tailor the treatment dose and interval, leading to a desired trough activity.

Kovaltry (Bayer HealthCare Pharmaceuticals) is a full-length, unmodified, recombinant human FVIII. The LEOPOLD clinical trial program assessed the PK, efficacy, and safety of Kovaltry.[7,8] A number of Kovaltry-specific popPK models are available for use on the WAPPS-Hemo platform for the purposes of Bayesian forecasting. The current study focuses on the qualification of this set of WAPPS-Hemo popPK models for treatment of Kovaltry patients, as well as the accompanying Bayesian forecasting method that estimates individual-specific PK parameters and concentration-time profiles. The qualification consists in assessing agreement of outcomes between Bayesian forecasting and noncompartmental analysis (NCA) with a subsequent limited sampling analysis on the Bayesian outcomes.

2 | METHODS

The qualification data set was obtained from a crossover PK study using Advate and Kovaltry by Shah et al.[9] Kovaltry one-stage and chromogenic assay factor activity and anthropometric data from patients enrolled and analyzed in Shah et al[9,10] were used for the analysis. The anthropometric data included body weight (median [min-max]: 80 [55-99] kg), body mass index (26.1 [18.5-28.9] kg/m^{-2}) and age (36 [19-64] years). Each of the 18 patients received a short-term intravenous infusion of 50 IU/kg. Plasma factor levels (IU/dL) were recorded before dosing; 15 minutes; 30 minutes; and 1, 3, 6, 8, 24, 30, and 48 hours after the administration of the dose, corresponding to 10 samples per infusion. No measurements were below the limit of quantification. Since these data had not been previously submitted to WAPPS-Hemo and therefore did not impact the development of the WAPPS-Hemo models, they were deemed appropriate for model qualification purposes.

The qualification procedure of the WAPPS-Hemo models consisted of two parts. Part 1, summarized in Table 1, involved the comparison of NCA outcomes to Bayesian predictions for the full, 10-sample per infusion, qualification data set. PopPK models used for Bayesian forecasting were the WAPPS-Hemo Kovaltry models (models A [one-stage] and B [chromogenic]). Since the NCA method is model independent,

TABLE 1 Agreement between evaluated and reference methods

Evaluation	Assay type	Evaluated model	Reference method/model	Half-life	Clearance
1) A vs NCA	One-stage	Model A: WAPPS-Hemo Kovaltry OS	NCA	R^2, .91 Bias, +3.0%	R^2, .99 Bias, +7.1%
2) B vs NCA	Chromogenic	Model B: WAPPS-Hemo Kovaltry CS	NCA	R^2, .89 Bias, +8.8%	R^2, .96 Bias, +10.5%

Abbreviations: CS, chromogenic substrate assay; NCA, noncompartmental analysis; OS, one-stage assay.

it was used as the reference comparator. Part 2 involved assessing PK prediction accuracy of reduced sampling scenarios for models A and B, each referenced to a dense 10-sample design.

2.1 | WAPPS-Hemo Models

The WAPPS-Hemo one-stage Kovaltry popPK model (model A) was built with a combination of industry (44%) and WAPPS-Hemo (56%) PK data, involving 293 patients ranging in age between 2.4 and 78.0 years. The WAPPS-Hemo chromogenic Kovaltry model (model B) was built with industry data only, involving 183 patients aged from 1 to 61 years.[11] Both models accounted for the same set of covariates comprising fat-free mass and age with interindividual variability on clearance and central volume of distribution, as well as interoccasion variability on clearance.[12]

2.2 | PK analysis

2.2.1 | Noncompartmental analysis

NCA was performed on the 18 patients from the Shah et al study using the *simbionca* toolbox from Matlab (R2017b, Mathworks, Natick, MA, USA) with default settings. The algorithm from the toolbox selected an optimal number of samples for the regression curve slope based on the quality of its fit. Clearance (CL; dL/h/kg) and half-life ($t_{1/2}$; hours) were derived for each patient using the full 10-point sampling data set. One-stage and chromogenic data were analyzed separately.

2.2.2 | Bayesian forecasting

Bayesian estimations were performed on the 18 patients from the Shah et al study[9] using NONMEM version 7.3 (ICON Development Solutions, San Antonio, TX, USA). The derived PK parameters through Bayesian forecasting in part 1 of this analysis were CL (dL/h/kg) and $t_{1/2}$ (hours), while the limited sampling analysis in part 2 also included time to 2% trough (TAT2; hours) and factor activity at 48 hours.

In part 2, the Bayesian predictions on the 18 patients were done under the full 10-point sampling scenario, which included FVIII activity measurements at the following time points: 10 time points given by predose; 15 minutes; 30 minutes; and 1, 3, 6, 8, 24, 30, and 48 hours (reference scenario). Evaluated reduced sampling scenarios accounted for predose plus a combination of either 2 or 3 additional time points from within 3-, 8-, 24-, 30-, and 48-hour samples.

2.3 | Statistical analysis

Statistical and graphical analyses were conducted in Matlab (R2017b). Agreement of the derived outcomes for evaluation, as compared to the reference, were measured by the coefficient of determination R^2 (Equation 1) and relative bias (Equation 2); where P_0 and P_1 represent the vectors of PK outcomes that were evaluated and used as reference, respectively, and where $\left(\frac{P_1 - P_0}{P_0}\right)$ is the corresponding relative error. Paired *t* tests were performed to assess if the mean of the paired differences between evaluation versus reference PK outcomes was zero.

$$R^2 = 1 - \frac{\text{variance}\,(P_1 - P_0)}{\text{variance}\,(P_0)} \tag{1}$$

$$\text{Relative Bias} = \text{mean}\left(\frac{P_1 - P_0}{P_0}\right) \tag{2}$$

3 | RESULTS

3.1 | Data

Figure 1 summarizes the factor activity versus time profiles for the 18 patients in Shah et al.[9] Wide interpatient variability is noted (eg, range at the first sample time: 40 to 78 IU/dL for chromogenic data, and 32 to 60 IU/dL for one-stage data). Median profiles suggest a similar decay rate between both measurement assays, with higher measured activities for the chromogenic assay (Figure 1).

3.2 | Part 1: Comparison between NCA and Bayesian forecasting

NCA estimations of $t_{1/2}$ were performed using a median [min-max] of 4 [3–9] samples for one-stage data and 5 [3–9] samples for chromogenic data. The corresponding regressions for the decay had $R^2 > .98$. There was a strong correlation between WAPPS-Hemo models A and B versus NCA-derived outcomes (Figures 2 and 3; upper panels). Relative errors were within ±25% for both PK outcomes with both assay types (Figures 2 and 3; lower panels), although there was a systematic trend of small positive relative errors for $t_{1/2}$ for the one-stage and CL and $t_{1/2}$ for the chromogenic model; central volume was also slightly higher in the case of the chromogenic model (data not shown). For the one-stage assay data, CL and $t_{1/2}$ had a relative associated bias of 7.1% and 3.0% and good correlation (Table 2: evaluation 1). In comparison, analogous assessment for the chromogenic assay data resulted in relative bias of 10.5% and 8.8% for CL and $t_{1/2}$, respectively (Table 2: evaluation 2). Although the relative error variability is considered low, the positive relative bias and consistent positive relative errors led to significant *t* test results associated with CL for model A versus NCA and both CL and $t_{1/2}$ for model B versus NCA (*P* values <.01).

3.3 | Part 2: Limited sampling analysis

Table 2 shows the coefficients of determination, R^2, of the PK outcomes obtained between full and reduced sampling schemes for

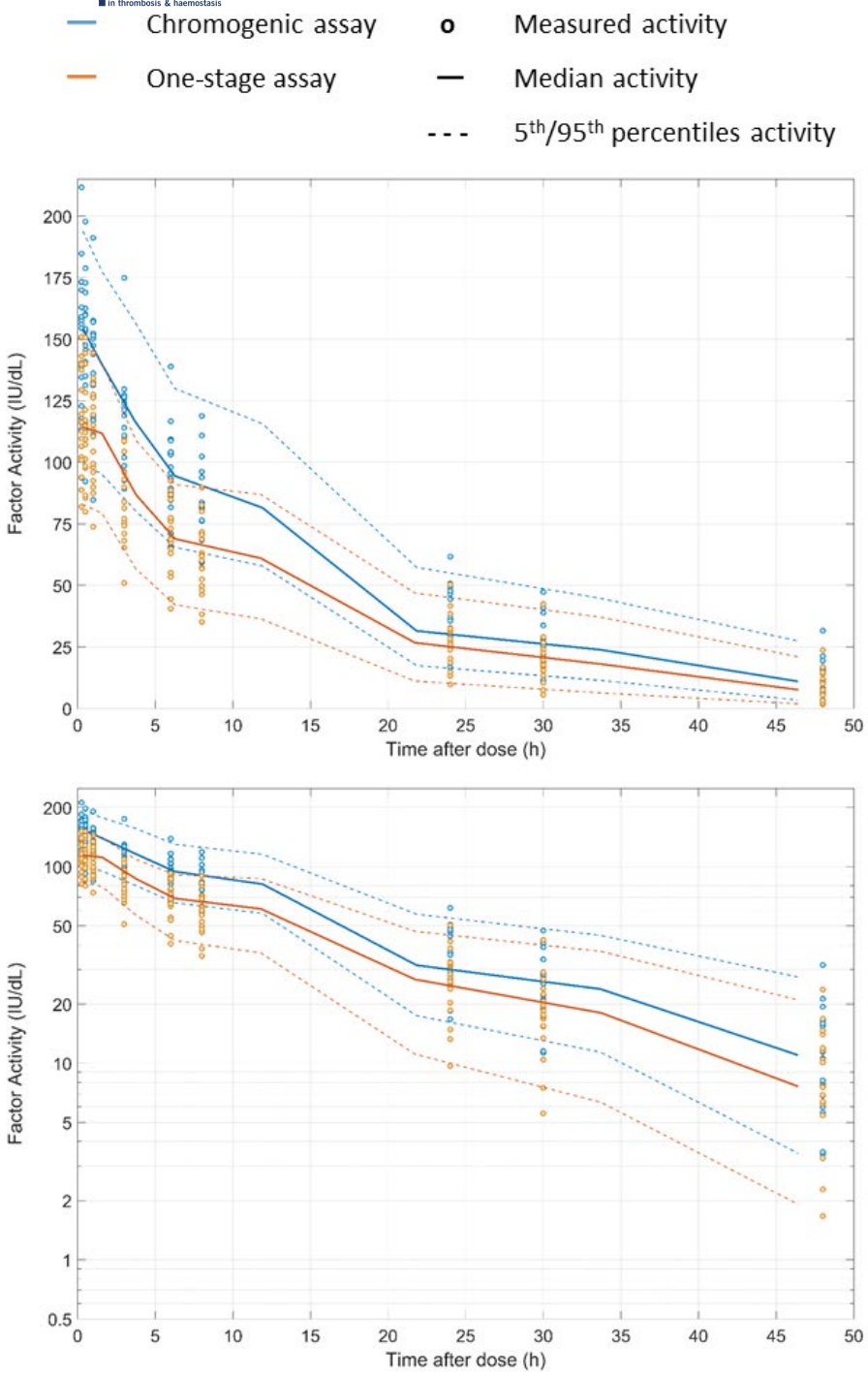

FIGURE 1 Factor activity vs time for chromogenic and one-stage data

models A and B. The WAPPS-Hemo–derived outcomes had a strong correlation between the full sampling scheme and the reduced four-sample schemes. There was a slightly weaker correlation between the full sampling and the reduced three-sample schemes.

For one-stage data, relative errors on $t_{1/2}$, CL, and TAT2 were consistently within ±25% for model A (Figure S1, four-sample schemes; Figure S3, three-sample schemes) with R^2 values ≥.88 (Table 2).

For chromogenic data, model B showed similar limited sampling results with relative errors consistently within ±25%; however, the error was slightly more spread and bias (Figure S2, four-sample schemes; Figure S4, three-sample schemes). Nonetheless, model B results were still reasonable with R^2 ≥ .84 for each tested sampling scheme and PK outcome (Table 2).

Irrespective of the model, prediction of factor activity at 48 hours showed greater relative error variability (Figures S1 to S4) especially for sampling schemes with earlier samples only. Since factor activities at 48-hour values are usually low (Figure 1), this PK outcome was more sensitive to the sampling scheme.

Limited sampling schemes that included a time point at 48 hours showed less error variability and bias for $t_{1/2}$ and TAT2. Indeed, for model A, R^2 for $t_{1/2}$ and TAT2 was ≥.99 when a 48-hour time point was included, while R^2 ranged from .88 to .97 when it was not.

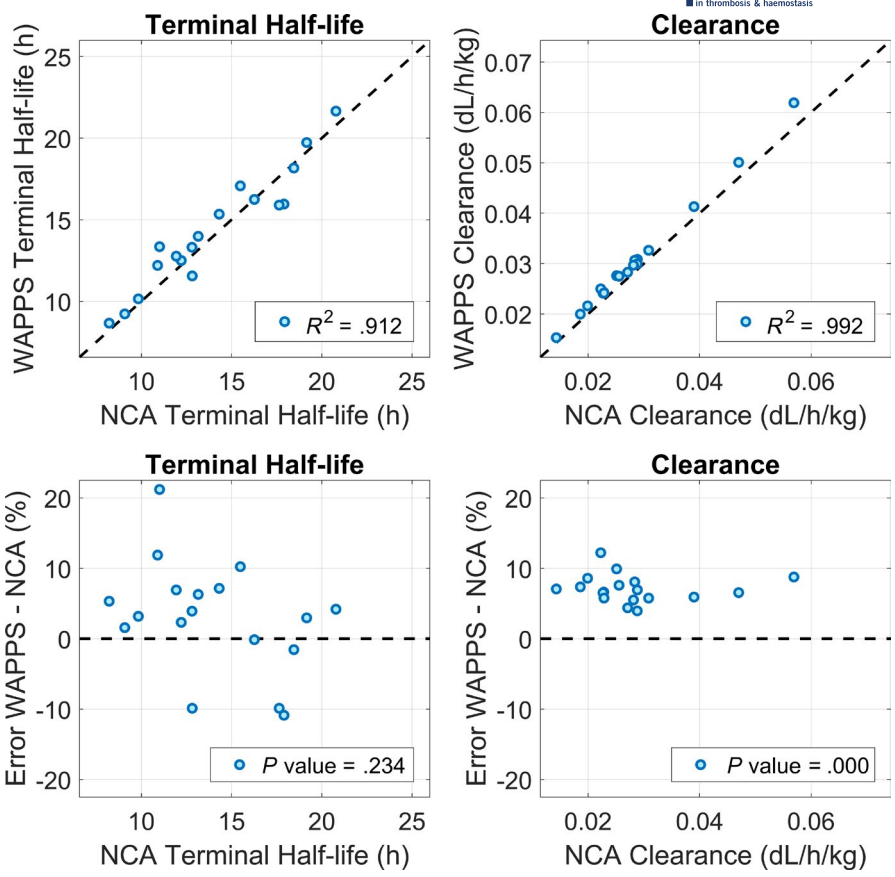

FIGURE 2 Comparison between PK parameters derived from NCA vs. PK parameters derived from WAPPS-Hemo Kovaltry model A (one-stage assay; full sampling scheme)

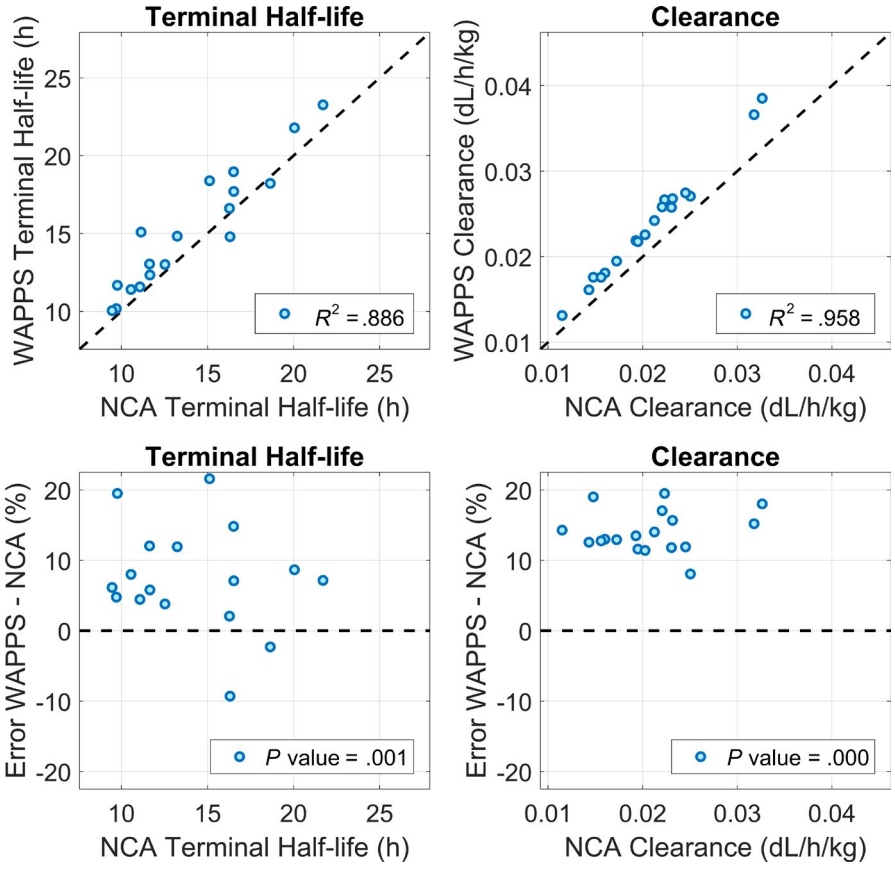

FIGURE 3 Comparison between PK parameters derived from NCA vs. PK parameters derived from WAPPS-Hemo Kovaltry model B (chromogenic assay; full sampling scheme)

TABLE 2 Agreement between dense and reduced sampling estimates represented by R^2 for models A and B

	Half-life		Clearance		TAT2	
Model	Model A	Model B	Model A	Model B	Model A	Model B
Reduced sampling scenario						
0–3–8-24 h	0.90	0.86	0.98	0.96	0.92	0.87
0–3–8-30 h	0.93	0.93	0.99	0.98	0.95	0.94
0–3–8-48 h	1.00	0.99	1.00	0.99	1.00	0.99
0–3–24-30 h	0.96	0.96	0.99	0.99	0.97	0.97
0–3–24-48 h	1.00	1.00	1.00	0.99	1.00	1.00
0–3–30-48 h	1.00	1.00	0.99	0.98	1.00	1.00
0–8–24-30 h	0.94	0.94	0.98	0.99	0.96	0.96
0–8–24-48 h	0.99	0.99	0.98	0.98	1.00	0.99
0–8–30-48 h	0.99	1.00	0.99	0.98	1.00	1.00
0–24–30-48 h	0.99	0.99	0.98	0.96	1.00	1.00
0–3-24 h	0.91	0.89	0.98	0.98	0.93	0.90
0–3-30 h	0.93	0.93	0.98	0.98	0.95	0.94
0–3-48 h	1.00	0.99	0.99	0.98	1.00	0.99
0–8-24 h	0.88	0.84	0.97	0.97	0.91	0.87
0–8-30 h	0.91	0.92	0.98	0.99	0.94	0.94
0–8-48 h	0.99	0.99	0.99	0.98	1.00	1.00
0–24-30 h	0.93	0.94	0.98	0.98	0.96	0.97
0–24-48 h	0.99	0.99	0.98	0.96	1.00	1.00
0–30-48 h	0.99	0.99	0.97	0.94	1.00	1.00

Abbreviation: TAT2, time above threshold of 2%.

Model B showed similar results with R^2 for $t_{1/2}$ and TAT2 ≥.99 when a 48-hour time point was included, while R^2 ranged from .86 to .97 when it was not.

4 | DISCUSSION AND CONCLUSION

This analysis sought to qualify popPK models developed by WAPPS-Hemo, and their use for Bayesian forecasting, in rich and sparse sampling scenarios. This qualification step is essential to the validation of such modeling and brings relevant information about outcomes reported by the WAPPS-Hemo platform.

As a first evaluation, this analysis compared clinically relevant PK outcomes obtained from dense sampling between NCA and Bayesian forecasting with brand-specific WAPPS-Hemo popPK models (models A and B). The comparisons of these methods on full sampling data showed a strong correlation. Bayesian methods showed some bias compared to NCA with a maximum relative error of 10.5% obtained for CL on chromogenic data. However, the relative error variability was low. To assess if this result was a function of the models that were used (A and B), Bayesian forecasting with literature models using the full sampling data was also performed (see Supporting Information) and confirmed the same results between Bayesian methods with literature models and NCA. By comparing Bayesian outcomes between models A and B and the literature models, there was almost no bias and very strong correlation leading to relative errors always ≤6.2% for every PK outcome. This suggests that regardless of the popPK model that was used in these assessments, with 10-sample observed data, the models provide almost identical outcomes since PK outcomes are primarily driven by the individual data and less so by the model.

This analysis relies on actual patient data from the Shah et al[9] publication. Consequently, the observations reflect true human variability in PK measurements even if the sample size (n = 18) may be more prone to lead to apparent bias between the methods. In particular, $t_{1/2}$ values estimated by NCA are derived from late samples and, as a consequence, may be sensitive to their measurement variability. The bias in $t_{1/2}$ estimates observed between NCA and the other analysis methods for the chromogenic assay data may have been influenced by the sample size associated with the methods' sensitivity to measurement variability.

As a second evaluation, the analysis compared clinically relevant PK outcomes obtained from Bayesian forecasting between different sampling strategies: The agreement between a full 10-point sampling scheme and a reduced 3- or 4-point sampling schemes was in a reasonable range (R^2 > .84). As expected, in each tested scenario, reduced sampling with only three observations led to slightly higher error variability as compared to reduced sampling with four observations that includes the three previous samples.

The limited sampling analysis brought interesting information to the interpretation of the Bayesian forecast in sparse sampling. The results support that early samples (before 30 hours) are less

informative for assessing $t_{1/2}$ and TAT2 as compared to later samples (48-hour time point). For most PK parameters, inclusion of a 48-hour sample improved the agreement between full and reduced sampling scenarios. Errors for $t_{1/2}$ and TAT2 were decreased by around two-fold each time a 24- or 30-hour sample was replaced by a 48-hour sample. Thus, PK parameters related to the terminal phase derived by WAPPS-Hemo models from early samples should be used with more caution than those derived from later samples, which can be used with more confidence. This is manifested on the WAPPS-Hemo platform, where PK outcomes are reported with credibility intervals. Credibility intervals for $t_{1/2}$ and time to outcomes will be wider when early samples are used for Bayesian forecasting as compared to the use of later samples. Regarding the number of samples, there was only a slight improvement in precision and bias when moving from three to four samples. The timing of the sampling was a more critical variable than the number of samples. These results support that popPK modeling can achieve precise PK estimates in limited sampling scenarios, decreasing patients' burden in clinical practice.

Although the one-stage assay is widely used for routine monitoring of people with hemophilia, the popularity of the chromogenic assay is increasing. There are a number of factor concentrate and nonfactor therapeutics (eg, bypassing agents, humanized bimimetic monoclonal antibodies) that must be uniquely considered when using different analyzers and one-stage reagents.[13] There are dozens of commercially available activated partial thromboplastin time reagents, each with a source of phospholipid and surface activator, such as silica, kaolin, or ellagic acid. Activators have the potential to cause inaccurate measurements when assaying vial potency or recovery of certain FVIII proteins. The buffer that is used for dilution may also introduce variability, and there are numerous commercially available buffers. Moreover, the analyzer used to assess clotting, which can be mechanical or optical, may introduce variability to the results as well.[13] It is prudent to understand when the one-stage assay may be prone to error for the above reasons, and when the chromogenic assay, which is less prone to variation, should be used in this modern era of hemophilia therapies.

This external qualification demonstrated that Bayesian forecasting, as performed by the WAPPS-Hemo platform, led to PK outcomes consistent with literature popPK models and that PK outcomes were still reasonably derived in a limited sampling environment, as evaluated on a population of actual patients. The results of this study support the utility of popPK and, specifically, the WAPPS-Hemo tool, to personalize prophylactic regimens for patients on Kovaltry. By using popPK and the sparse sampling protocol, clinicians are empowered to offer patients a less burdensome sampling method, requiring 3 to 4 rather than 10 blood draws.

AUTHOR CONTRIBUTIONS

All authors contributed to the concept and design of the manuscript. PC and DH performed the analysis. PC, DH, AE, and JS interpreted the data. All authors participated in writing or revising the intellectual content and final approval of the version to be published.

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PC has received a grant from Bayer; MM and JS are employees of Bayer; SY is an employee and shareholder of Bayer; AI's institution has received project-based funding via research or service agreements from Bayer, CSL, Grifols, NovoNordisk, Octapharma, Pfizer, Roche, Sanofi, Sobi, Spark, Takeda, and Uniqure; AE has received speaking fees and institutional funding from Bayer; DH has no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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