Population pharmacokinetic characterization of BAY 81-8973, a full-length recombinant factor VIII: lessons learned – importance of including samples with factor VIII levels below the quantitation limit

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Introduction: The pharmacokinetics (PK), safety and efficacy of BAY 81-8973, a full-length, unmodified, recombinant human factor VIII (FVIII), were evaluated in the LEOPOLD trials. Aim: The aim of this study was to develop a population PK model based on pooled data from the LEOPOLD trials and to investigate the importance of including samples with FVIII levels below the limit of quantitation (BLQ) to estimate half-life. Methods: The analysis included 1535 PK observations (measured by the chromogenic assay) from 183 male patients with haemophilia A aged 1–61 years from the 3 LEOPOLD trials. The limit of quantitation was 1.5 IU dL⁻¹ for the majority of samples. Population PK models that included or excluded BLQ samples were used for FVIII half-life estimations, and simulations were performed using both estimates to explore the influence on the time below a determined FVIII threshold. Results: In the data set used, approximately 16.5% of samples were BLQ, which is not uncommon for FVIII PK data sets. The structural model to describe the PK of BAY 81-8973 was a two-compartment model similar to that seen for other FVIII products. If BLQ samples were excluded from the model, FVIII half-life estimations were longer compared with a model that included BLQ samples. Conclusions: It is essential to assess the importance of BLQ samples when performing population PK estimates of half-life for any FVIII product. Exclusion of BLQ data from half-life estimations based on population PK models may result in an overestimation of half-life and underestimation of time under a predetermined FVIII threshold, resulting in potential underdosing of patients.

Keywords: clinical trials, haemophilia A, half-life estimation, population pharmacokinetics, recombinant FVIII, simulation

Introduction

Treatment of patients with haemophilia A involves the use of replacement factor VIII (FVIII) products either on demand or prophylactically to prevent bleeding episodes. Increased time spent below a certain FVIII activity level is considered one of the important determinants of breakthrough bleeding risk during prophylaxis [1]. The time spent below a given FVIII threshold is determined by the pharmacokinetic (PK) parameters of the FVIII products, which can vary among patients [2]. Population PK modelling approaches can be useful in identifying patient characteristics that influence PK and can be applied to derive dosing regimens that minimize the time below a desired FVIII threshold [3]. PK parameters in individual patients can be estimated using sparse sampling and Bayesian analysis; thus, population PK modelling can reduce the number of blood samples needed for PK-based dosing regimens [3,4]. These population PK models are especially useful for combining data from multiple studies, which may differ with regard to study design, dose and dosing frequency of the FVIII product, sampling time schemes, and/or study population (e.g. adults vs. children) [5].

BAY 81-8973 (Kovaltry®, Bayer HealthCare Pharmaceuticals, Berkeley, CA, USA) is a full-length, unmodified, recombinant human FVIII. PK, efficacy and safety of BAY 81-8973 were evaluated in the Long-Term Efficacy Open-Label Program in Severe
Hemophilia A Disease (LEOPOLD) clinical trials in children, adolescents and adults with severe haemophilia A [6–8]. Key PK results from the three trials have been previously reported and indicated a more favourable PK profile for BAY 81-8973 vs. sucrose-formulated recombinant FVIII (rFVIII-FS) [9].

The aim of this study was to develop a population PK model for BAY 81-8973 based on pooled data from the 3 LEOPOLD trials and to investigate the importance of including samples with FVIII levels below the limit of quantitation (BLQ) on the half-life estimates and time below FVIII threshold.

Methods

Included studies

The population PK analysis included data from patients enrolled in the 3 LEOPOLD trials. Patients with severe haemophilia A (defined as <1% FVIII activity as determined by one-stage clotting assay) aged 12–61 years (LEOPOLD I and II) or ≤12 years (LEOPOLD Kids, part A) with ≥150 (LEOPOLD I and II) or ≥50 (LEOPOLD Kids, part A) exposure days to any FVIII product and no history of FVIII inhibitors were included [6–8].

Population modelling

The PK model was developed using dense PK samples (10 and 4 PK samples following an infusion in adults and children respectively) from all 183 patients in the three studies, using the chromogenic assay. The limit of quantitation was 1.5 IU dL⁻¹ in general and 3 IU dL⁻¹ for a small number of samples. Dosing information was based on the chromogenic assay [6,7].

Mixed-effects modelling methods as implemented in NONMEM® (version 7, level 2.0; ICON, Hanover, MD, USA) were used. A mixed-effect model includes two kind of effects: (i) fixed effects; the structural model contains descriptors of a process (e.g. PK parameters like clearance [CL] and volume of distribution); and (ii) random effects; the random model has two sources of variability, interindividual or between-subject variability (describing the fact that structural PK parameters like CL vary among individuals) and residual error or noise (e.g. the error in the analytic assay).

Between-subject variability (BSV) was estimated using the following model:

\[ P_i = P_{\text{pop}} \cdot e^{\eta_i} \]

Here \( P_i \) represents the individual pharmacokinetic parameter for the \( i \)th individual and \( \eta_i \) represents the independent random variable with a mean of 0 and variance \( \sigma^2 \). This model assumed a log normal distribution for the \( P_i \) values and a normal distribution of \( \eta_i \) values. Residual unexplained variability (RUV) was tested as either an additive error, proportional error, or combined additive and proportional error and selected based on the assessment of goodness-of-fit plots and the objective function (OBJ) such that:

\[ C_{ij} = \hat{C}_i \cdot (1 + e_{ij}) + e_{ij} \]

Here, \( C_{ij} \) is the \( i \)th observation in the \( j \)th individual, \( \hat{C}_i \) is the model prediction for the \( i \)th observation in the \( j \)th individual, \( e_{ij} \) is the proportional RUV and \( e_{ij} \) is the additive RUV with means of 0 and variances of \( \sigma^2_1 \) and \( \sigma^2_2 \) respectively.

Models were fit to untransformed data using the first-order conditional estimation (FOCE) method in NONMEM with the INTERACTION option (for data above the lower limit of quantitation [LLOQ] only), and the M3 method (all data including BLQ data) [10] using Laplace with the SLOW and INTERACTION options. Data management, graphical analysis and model postprocessing were performed using R (version 2.13.0) [11].

Structural model development was guided by graphical and numerical techniques. Numerical techniques include assessment of the change (Δ) in OBJ. ΔOBJ was used to determine the statistical significance between the fit of two nested models to the data, assuming a chi-square distribution for ΔOBJ. A ΛOBJ ≥ 7.9 (\( P < 0.005 \)) was considered significant when comparing models that differed by 1 structural model parameter.

Covariate model building

Covariates were tested with stepwise forward inclusion/backward deletion covariate modelling [12,13] using standard significance levels for selection or deletion of covariates with ΔOBJ ≥ 6.63 (\( P < 0.01 \)) for forward selection and OBJ ≥ 7.9 (\( P < 0.005 \)) for backward elimination respectively. The forward selection process included covariates in order of effect on OBJ. Covariates assessed included age, height, weight, body mass index (BMI) and lean body weight (LBW) at baseline, as well as race. Covariates were modelled as changes in a given parameter from the reference patient (i.e. patient with demographic factors equal to the median [for continuous covariates] or most prevalent [for categorical covariates]). Covariates were normalized to population median values with continuous covariates modelled using the following general equation:
\[ TV \, P_i = P_{\text{pop}} \cdot \left( \frac{\text{cov}_i}{\text{cov}_{\text{med}}} \right)^\theta \]

Here, \( TV \, P_i \) represents the model-predicted PK parameter for the typical individual with covariate value \( \text{cov}_i \), \( P_{\text{pop}} \) represents the population central tendency for the PK parameter \( TV \, P \) and \( \text{cov}_{\text{med}} \) represents the population median value of the covariate. \( \theta \) represents the scale factor.

Race was modelled using the following equation:

\[ TV \, P_i = P_{\text{pop}} \cdot \theta^{\text{cov}}. \]

Here, \( \theta \) describes the change in parameter relative to the reference subgroup.

If \( \geq 2 \) significant covariates identified during the univariate analysis were highly correlated, only 1 covariate was tested in the full model (applied for covariates describing size [weight, BMI and LBW]).

**Pharmacokinetics model evaluation**

Simulation characteristics of the model were assessed using visual predictive checks (VPCs). The 5th, 50th and 95th prediction intervals were determined from simulations of concentration-time data from the posterior distribution of the model. The 5th, 50th and 95th percentiles computed from observed data were overlaid on simulated prediction intervals. If a strong covariate effect was identified in the model, data were stratified with respect to the specific covariate. If the model described the data with good precision, observed and simulated percentiles were closely aligned.

**Simulation of pharmacokinetics parameters**

Using the final model, individual PK parameters CL and volume of distribution at steady state were estimated for patients in the LEOPOLD trials from which the area under the curve and half-life were calculated. The individual PK parameters are maximum a posteriori Bayesian (MAPB) estimates from a prior parameter distribution using the population estimates of the population mean of the parameter, the BSV in the parameter and the uncertainty.

**BAY 81-8973 simulations with and without inclusion of samples below the limit of quantitation**

Factor VIII half-life following BAY 81-8973 administration was estimated in the population PK analysis using models that did not include BLQ samples (non-M3) and models that included BLQ samples (M3). Simulations were conducted with both estimates to determine the influence on time below FVIII threshold with dosing regimens of 25 and 50 IU kg\(^{-1}\) FVIII twice weekly.

**Results**

**Patients and pharmacokinetics data set**

Baseline demographics and covariate characteristics of 183 patients with haemophilia A from the 3 LEOPOLD trials included in the population PK analysis (including 51 patients aged 1–11 years) are shown in Table 1. A total of 1535 chromogenic assay observations were included in the analysis. In total, 16.5% of PK samples were BLQ. Although the BLQ samples accounted for 16.5% of the overall data, this percentage increased to >90% at the terminal part of the FVIII curve. The increase in the proportion of BLQ samples is illustrated in Fig. 1.

**Development of base model**

Modelling was initially performed using only measurable observations (BLQ data excluded); the best base model was a two-compartment model. However, the resulting half-life was unrealistically long. An in-depth evaluation showed that without inclusion of BLQ information, half-life estimation was biased in the direction of a longer half-life. Therefore, the M3 method [10] was used. When BLQ observations were considered, all parameters were similar to those with the non-M3 method with the exception of peripheral volume of distribution (\( V_p \)), which was reduced by more than half (~18 to ~7 dL), resulting in a decreased terminal elimination half-life. The terminal half-life estimate for BAY 81-8973 was 18.9 and 13.9 h using the non-M3 and M3 models respectively. The latter estimate is consistent with the half-life of 13.8 h derived from a non-compartmental analysis of densely sampled BAY 81-8973 PK data [9].

Because LBW appeared to have a very strong relationship with both CL and central volume of distribution (\( V_c \)), this covariate relationship had to be included in the base model for stability. All parameters were estimated well for this model with good standard errors.

**Table 1. Baseline demographics of the patient population used for the BAY 81-8973 population PK model.**

| Age, years | Mean ± SD (% CV) | Median (range) | Patients, n |
|------------|------------------|----------------|-------------|
| Race       |                  |                |             |
| White      | —                | —              | 132         |
| Asian      | —                | —              | 31          |
| Black      | —                | —              | 10          |
| Hispanic   | —                | —              | 9           |
| Other      | —                | —              | 1           |
| Height, cm | 160 ± 25.8 (16.2)| 170 (74–192)   | 182         |
| Weight, kg | 57.7 ± 24.8 (43)| 60 (11–124)    | 183         |
| BMI, kg m\(^{-2}\) | 21.3 ± 5.14 (24.2) | 20.4 (13–38.3) | 182 |
| LBW, kg    | 46.2 ± 16.7 (36.1)| 51.3 (9.23–79.2)| 182 |

**Notes:**

BMI, body mass index; CV, coefficient of variation; LBW, lean body weight; PK, pharmacokinetics.
The base model for BAY 81-8973 (Fig. 2) was a two-compartment model with combined RUV. Parameter estimates for the model are shown in Table 2. A nonlinear positive correlation between CL and LBW was observed with an estimated exponent of 0.610 (95% CI, 0.45–0.75), whereas V_C was almost linearly related to LBW, with an estimated exponent of 0.950 (95% CI, 0.890–1.02). All parameters were estimated well for this model with good standard errors (coefficient of variation <21.9% for fixed effects, <38.4% for random effects).

**Base model**

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**Covariate analysis and final model**

In the univariate analysis, LBW was found to be the most significant size descriptor for inclusion on CL and V_C and was already included in the model during base model development. Age was strongly correlated with LBW, and its addition to the model did not result in further improvement of model fit. The distribution and correlation of size-related covariates is presented in Fig. 3. The only other significant covariate detected in the forward selection was Asian race on V_C (ΔOBJ ≥ 6.63; P < 0.01). However, because its removal from the multivariate model resulted in an increase in OBJ of 6.68 points (not significant based on the predefined level), it was not retained in the final model. With inclusion of LBW as covariate in the final BAY 81-8973 model, a lack of relationship between the remaining random effects for CL and V_C vs. LBW was observed (Fig. 4a), demonstrating correct implementation of the LBW effect. After covariate analysis, a covariance term between CL and V_C vs. LBW in the final model is shown in Fig. 4b. To re-assess the effect of excluding BLQ on parameter estimation, the final model parameters (including the covariate relationships) were then re-estimated without consideration of BLQ values; this resulted in the same half-life over prediction as observed during model development. A parameter comparison of both models is presented in Table 3.

**Model qualification**

As indicated by VPCs (Fig. 5), the final model predicted the observed data well over the entire concentration and time range and could be used for simulation purposes.

**Simulations of pharmacokinetics parameters**

The PK parameters estimated for all patients in the LEOPOLD programme based on the final model are shown in Table 4.
Simulations demonstrating importance of considering samples below the limit of quantitation

Simulations based on half-life estimates of BAY 81-8973 from the non-M3 and M3 models illustrated the effect of different PK parameter estimates on expected time under various FVIII thresholds (Table 5). Based on a terminal half-life of 18.9 h (non-M3 model), the expected time under a threshold of 1 IU dL\(^{-1}\) for a...
simulated twice-weekly dose of 25 IU kg\(^{-1}\) was ~3 h week\(^{-1}\) compared with ~21 h week\(^{-1}\) for a half-life of 13.9 h (M3 model; Table 5 and Fig. 6).

**Discussion**

Although population PK models can provide valuable information, PK results obtained from different FVIII models from publications need to be carefully evaluated. Excluding BLQ samples from analysis may not be an issue when the proportion of BLQ samples is minimal (~5\%) or if the detection limit is very low. However, in the presence of high numbers of BLQ samples or a high detection limit, excluding BLQ samples can result in a significant bias in the fit of population PK models [10]. The comparison of the model parameter estimates of both models (including covariates) shows that the downward bias in clearance (~50\% peripheral, ~10\% central), and upward bias in peripheral volume (~50\%, Table 3) results in an overestimation of the terminal half-life. If a substantial number of samples are BLQ in the terminal phase of a PK profile, excluding them will result in a terminal phase consisting only of measurable samples (reflective of patients with a low CL), resulting in a bias towards a longer half-life estimation. In other words, if many of the PK samples taken late (in the terminal phase) are BLQ and if these BLQ samples are excluded from the analyses, the model can only consider information from patients with a low CL to estimate the population parameter. This can lead to a bias in the different population PK parameters, as confirmed in the current analysis. Furthermore, simulation studies showed a lower expected time under a given FVIII threshold when FVIII half-life was calculated with the exclusion of BLQ samples. This might have direct relevance for treatment because PK-guided dosing approaches are often based on estimated individual or population half-lives determined using population PK models. The goal of such PK-guided dosing approaches is to lower the frequency of FVIII administration or reduce time spent below a FVIII threshold.

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**Table 3.** Comparison of PK parameters of the BAY 81-8973 model considering only samples above LLOQ or including BLQ samples.

| Parameter       | Estimate not using M3 | Estimate using M3 (final model) |
|-----------------|------------------------|---------------------------------|
| CL, dL h\(^{-1}\) | 1.69                   | 1.88                            |
| LBW on CL       | 0.704                  | 0.610                           |
| CL\(_{\text{int}}\), dL h\(^{-1}\) | 0.981                  | 1.90                            |
| V\(_c\), dL      | 30.6                   | 30.0                            |
| LBW on V\(_c\)   | 0.912                  | 0.950                           |
| V\(_p\), dL      | 9.80                   | 6.37                            |
| Derived parameters |                        |                                 |
| Initial half-life, h | 4.60                   | 1.85                            |
| Terminal half-life, h | 18.9                   | 13.9                            |

CL, clearance; CL\(_{\text{int}}\), intercompartmental CL; LBW, lean body weight; M3, includes samples below the limit of quantitation; V\(_c\), central volume of distribution; V\(_p\), peripheral volume of distribution.
threshold (e.g. 1 IU dL\(^{-1}\)), which is thought to be related to the bleeding rate [1]. Thus, this analysis highlights the importance of including BLQ samples in population PK models to avoid biasing FVIII half-life estimates. The final structural model chosen to describe BAY 81-8973 PK included all available information, including BLQ data.

This study and other previously published studies report LLOQ values ranging from 0.5 to 1.5 IU dL\(^{-1}\) for PK measurements across various FVIII products [14–16]. Despite minor differences in the exact LLOQ values reported with varying assay methodologies, the presence of BLQ samples is common in other PK studies with FVIII products [16]. In this study, the population PK analysis with BAY 81-8973 is used as an example to show the importance of including BLQ samples in the population PK model; this approach is relevant for obtaining accurate results for all FVIII activity measurements irrespective of assay methodology with a comparable LLOQ. Assays with a much lower LLOQ would potentially reduce the problem as detected in the current population PK analysis. However, such assays are not yet commercially available.

In the current analysis of pooled data from the LEOPOLD studies, PK of BAY 81-8973 was best described by a two-compartment model. A biphasic profile is typically seen for FVIII [5,17]. The first part of the concentration-time profile most likely reflects a fast distribution compartment (0–2 h after dose).

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**Table 4.** PK parameter estimates based on empirical Bayes estimates for all patients in the LEOPOLD trials.

| PK parameter, geometric mean (%CV) | 18 years | 12–18 years | 6–12 years | 0–6 years |
|-----------------------------------|----------|-------------|------------|----------|
| AUC, IU h dL\(^{-1}\)* | 1858 (38) | 1523 (27) | 1242 (35) | 970 (25) |
| CL, dl h\(^{-1}\) kg\(^{-1}\) | 0.03 (38) | 0.03 (27) | 0.04 (35) | 0.05 (25) |
| \(V_{ss}\), dl kg\(^{-1}\) | 0.56 (14) | 0.61 (14) | 0.77 (15) | 0.92 (11) |

AUC, area under the curve; CL, clearance; CV, coefficient of variation; LEOPOLD, Long-Term Efficacy Open-Label Program in Severe Hemophilia A Disease; PK, pharmacokinetics; \(V_{ss}\), volume of distribution at steady state.

*AUC calculated for a dose of 50 IU kg\(^{-1}\).
administration), estimated as $V_p$, which is rarely seen for small molecules. This is speculated to be the result of a fast binding process within plasma (e.g. to von Willebrand factor) because the overall volume of distribution ($V_c + V_p$) is close to plasma volume. The results are in line with published data; in a study with another FVIII compound, the authors found a very similar PK profile as seen in this study, with a small peripheral distribution compartment, larger central compartment and overall volume of distribution close to plasma volume [5]. The study reported a population CL of 1.93 dL h$^{-1}$, $V_c$ of 22.2 dL, $V_p$ of 7.3 dL, intercompartmental CL ($CL_p$) of 14.7 dL h$^{-1}$ and a non-linear relationship with body weight [5].

Moreover, the predicted PK parameters described in Table 4 are similar to the PK parameters for patients with dense PK samples and calculated using the non-compartmental method. For example the geometric mean AUC for 26 patients with dense PK data was 1890 IU h dL$^{-1}$ using non-compartmental analysis [9] compared with the value of 1858 IU h dL$^{-1}$ for patients aged >18 years based on the simulations.

LBW was the only significant covariate found to strongly influence the CL and $V_c$ of BAY 81-8973. Because of the ~10-fold difference in size of patients (1–61 years) in the three trials, with weight ranging from 11 to 124 kg and LBW ranging from 9.25 to 79.2 kg, LBW was included during structural model development. LBW had a close to linear correlation with $V_c$ and a positive non-linear relationship with CL. The only other potential covariate effect identified during modelling was of Asian race on $V_c$; however, this relationship was only statistically significant in the forward inclusion step and did not reach the statistical significance required to be retained during the backward elimination procedure. It could be speculated that the mathematical relationship, although providing adequate description, is not a 100% accurate for Asian patients considering the limited number of Asian patients (17%) in the data set.

It should be noted that some of the observed variability in CL and $V_c$ was also influenced by age in a univariate analysis; however, age was highly correlated with LBW. In the multivariate analysis, age was no longer significant when LBW on CL was included in the model, confirming that LBW accounted for all variability in CL attributable to age. No other covariates were found to be significant. Thus, the base model with LBW on CL and $V_c$ was the final model for BAY 81-8973. VPCs indicated that performance of the final model was good and could describe the data with limited bias and good precision.

### Table 5. Estimated time spent below various FVIII thresholds from simulations with BAY 81-8973.

| FVIII Threshold | 1 IU dL$^{-1}$ | 3 IU dL$^{-1}$ | 5 IU dL$^{-1}$ |
|----------------|---------------|---------------|---------------|
| BAY 81-8973    | M3            | Non-M3        | M3            | Non-M3        | M3            | Non-M3        |
| 25 IU kg$^{-1}$ | Mean h week$^{-1}$ | 31           | 14           | 59           | 44           | 77           | 66           |
|               | Median h week$^{-1}$ | 21           | 3            | 62           | 41           | 83           | 69           |
|               | 95% range, h week$^{-1}$ | 0–97         | 0–68         | 0–120        | 0–110        | 0–130        | 0–120        |
| 50 IU kg$^{-1}$ | Mean h week$^{-1}$ | 18           | 5.5          | 39           | 22           | 54           | 37           |
|               | Median h week$^{-1}$ | 8            | 0            | 35           | 15           | 56           | 33           |
|               | 95% range, h week$^{-1}$ | 0–82         | 0–45         | 0–100        | 0–82         | 0–120        | 0–98         |

FVIII, factor VIII; M3, includes samples below the limit of quantitation; non-M3, does not include samples below the limit of quantitation.

*Simulated administration occurred every Monday and Thursday morning.
In patients with haemophilia, the prevalence of obesity is on the rise [18]; however, there are no specific guidelines for dosing of replacement factors in obese patients with haemophilia. Standard weight-based dosing approaches may result in underdosing or overdosing [19]. In obese patients, ideal-body-weight–based dosing or LBW-based dosing may be an alternate approach [19]. LBW can be a surrogate for fat-free mass and might better explain the observed FVIII concentrations in obese patients because FVIII is mainly distributed in plasma. Accordingly, predictive PK models for other drugs have found LBW to be a more suitable covariate compared with total body weight in an obese patient population [20].

In children, LBW and body weight are highly correlated and this does not explain the slightly lower exposure observed in this patient group. Two aspects influence the lower exposure in children: (i) growth of children influencing the CL capacity; and (ii) the biphasic profile of FVIII and the related volume of distribution. For many products, CL is related to the growth and resulting size of children. This relationship with size-related parameters (e.g. LBW, body surface area) is known to be non-linear and is typically described by allometric scaling. This allometric relationship has been reported for other FVIII products [5,17] and was confirmed for BAY 81-8973. The non-linear relationship of weight (or LBW) with CL results in the highest CL per unit of (lean) body weight (CL kg⁻¹) in the lightest, and therefore youngest, children. Dosing by body weight assumes a linear increase in CL in relationship with body weight in children, thus leading to overcorrection of CL and a resultant slightly lower exposure in children vs. adults; in fact, the real CL kg⁻¹ in children is higher than assumed. In general, the change in volume of distribution with age can be directly related to weight (or LBW). Therefore, weight-based dosing is generally acceptable in children to correct for volume of distribution, assuming a linear relationship. However, FVIII shows a biphasic PK profile, and the first part of the concentration-time profile does not scale linearly [5,17]. Although the influence of this phenomenon on exposure might be low, it can potentially result in higher volume of distribution, slightly lower initial concentration and lower recovery in children. It should be noted that in general, a normalization of PK parameters by body weight for illustrations should be avoided for FVIII, especially if children, lean patients, or obese patients are compared. For example adjusting the volume of a 100-kg patient and a 20-kg patient by body-weight would result in misleading comparisons.

In a meta-analysis of 121 population PK studies that explored the use of body size covariates in PK analyses, LBW with an allometric exponent of ~2/3 was found to best describe drug CL across body sizes because it accounts for both allometric scaling from children into adults and variability in body composition [21]. The results of the current PK analysis are consistent with the results of this meta-analysis.

Conclusion

This study shows the importance of including BLQ samples in estimation of population PK half-lives of FVIII products. If BLQ samples are excluded from population PK models for FVIII, the half-life estimations using the model can result in an overestimation of half-life and underestimation of time under a FVIII threshold. The population PK model for BAY 81-8973 based on the 3 LEOPOLD trials included the BLQ samples in the data set; it was a two-compartment model with a strong relationship between LBW and both CL and Vc. The model indicates a potential to improve dose adaptions if LBW and allometric principles are considered instead of a linear body-weight based correction of the FVIII dose.

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