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LETTER TO THE EDITOR

Population pharmacokinetic (PopPK) modelling indicates that patients switching to BAY 81-8973 from rFVIII-FS can continue their dosing schedule with improved protection

BAY 81-8973 (Kovaltry, Bayer, Berkeley, CA, USA) is an unmodified, full-length, recombinant factor VIII (rFVIII). It has the same primary amino-acid sequence as sucrose-formulated rFVIII (rFVIII-FS; Kogenate); however, BAY 81-8973 is produced using advanced manufacturing methods.[1] BAY 81-8973 has demonstrated efficacy and a good safety profile for the prevention and treatment of bleeding episodes in children, adolescents and adults with severe haemophilia A.[2-4] In addition, in an interindividual crossover study, BAY 81-8973 was shown to have a longer half-life, higher area under the curve (AUC) and lower clearance than rFVIII-FS.[5] The improved pharmacokinetic (PK) properties of BAY 81-8973 appear to be related to its greater level of N-linked glycan branching and sialylation compared with other full-length rFVIII products, which prolongs the time that it remains in circulation.[6] These properties of BAY 81-8973 have also been confirmed in a real-world study.[7]

In haemophilia treatment, population pharmacokinetics (popPK) modelling has been successfully utilized to predict a patient's individual PK profile, including trough factor levels, based on few measurements only, and can be a convenient approach to support treatment.[8]

Simulations based on a popPK analysis of data from a phase 1 crossover study showed that BAY 81-8973 has an improved PK profile compared with the recombinant antihaemophilic factor plasma/albumin-free method (rAHF-PFM), with lower doses of BAY 81-8973 vs rAHF-PFM needed to achieve the same FVIII trough levels.[9] The aim of the present study was to predict the interindividual differences when switching from rFVIII-FS to BAY 81-8973, using a popPK model based on data collected in the crossover study. These results might be useful to guide dosing and scheduling when switching from rFVIII-FS to BAY 81-8973 treatment.

Twenty-six patients were treated in a randomized, interindividual, crossover design study, starting with either 50 IU/kg of BAY 81-8973 or rFVIII-FS followed by frequent PK sampling over 48 hours.[5] Between the two administrations, a wash-out period of at least 72 hours was requested. Full details of the study design, simulation methodology and statistical analyses have previously been published.[5,9]

A popPK model was developed considering similarities and dissimilarities in PK between the two products using statistical significance criteria. The popPK analysis was conducted using NONMEM (version 7, level 2.0; ICON, Hanover, MD, USA). Using the developed popPK model, and based on the study patients, half-life and predicted trough levels of BAY 81-8973 vs rFVIII-FS administered twice-weekly or three-times-weekly at steady state were estimated for different doses. In addition, the model was used to predict the time to reach FVIII threshold levels of 1, 3, 5 and 10 IU/dL. In addition, for each patient, the doses required to maintain FVIII level always above the threshold level of 1 IU/dL for a twice-weekly and three-times-weekly schedule were predicted.

A two-compartment model was found to adequately describe the PK of both BAY 81-8973 and rFVIII-FS. Statistically significant differences ($P < .01$) in the structural popPK model parameters between BAY 81-8973 and rFVIII-FS were only identified in the clearance. Simulations based on the popPK model showed that trough levels for all patients were higher with BAY 81-8973 compared with rFVIII-FS at steady state after a dose of 30 IU/kg twice-weekly and three-times-weekly (data not shown).[9] The improvement in PK seen with BAY 81-8973 vs rFVIII-FS was also found to be consistent across study patients (data not shown).

TABLE 1 Median time to factor VIII threshold after single intravenous dose (simulated data)

Dose IU/kg	Threshold level IU/dL	BAY 81-8973 h	rFVIII-FS h	Absolute difference h
25	1	77.0	66.5	10.5
25	3	54.5	47	7.5
25	5	44.0	37.5	6.5
25	10	30.0	25	5.0
30	1	81.0	70	11.0
30	3	58.5	50	8.5
30	5	48.0	41	7.0
30	10	33.5	28.5	5.0
50	1	91.0	79	12.0
50	3	69.0	59	10.0
50	5	58.5	50	8.5
50	10	44.0	37.5	6.5

Abbreviation: rFVIII-FS, sucrose-formulated recombinant factor VIII.

TABLE 2 Percentage of patients maintaining factor VIII levels >1 IU/dL (simulated data)

	2×/wk Regimen			3×/wk Regimen		
Dose IU/Kg	BAY 81-8973	rFVIII-FS	Difference[a]	BAY 81-8973	rFVIII-FS	Difference[a]
25	25.0	12.4	12.6	61.8	44.1	17.7
30	30.6	16.7	13.9	67.8	48.9	18.9
50	44.9	26.1	18.8	81.3	65.2	16.1

Abbreviation: rFVIII-FS, sucrose-formulated recombinant factor VIII.

[a]Percentage difference between BAY 81-8973 and rFVIII-FS

Based on in silico simulations of a virtual patient population (n = 1000), time to 1 IU/dL was predicted to be ~16% (~10 hours) longer for BAY 81-8973 compared with rFVIII-FS over a dose range of 25-50 IU/kg (Table 1). The proportion of patients that reached a FVIII level >1 IU/dL was higher with BAY 81-8973 at both dosing frequencies (Table 2) and was achieved by a lower weekly dose compared with rFVIII-FS. Based on twice-weekly dosing, the dose required to maintain FVIII plasma levels >1 IU/dL in at least 50% of patients on BAY 81-8973 vs rFVIII-FS was 59.5 and 124 IU/kg, respectively.

In the current study, simulations using the popPK model showed that median time to a trough level of 1 IU/dL FVIII was longer for BAY 81-8973 vs rFVIII-FS and that a lower dose of BAY 81-8973 vs rFVIII-FS was needed to achieve a threshold of 1 IU/dL FVIII.

This PK profile is consistent with clinical trial data that have shown an improved PK with BAY 81-8973 compared with rFVIII-FS, as well as observations in a real-world study that concluded that switching from rFVIII-FS to BAY 81-8973 can be performed easily without risks to patients.[3,10] Results from this popPK model expand on previous findings[8] and suggest that patients who switch to BAY 81-8973 can remain on the same dosing frequency and are likely to achieve higher FVIII levels and improved protection.

An important consideration is that this simulation is based on the concentrations measured using the chromogenic assay, whereas the one-step assay is more commonly used in clinical practice. Although this may cause variation in quantitative readouts compared with real-world data, it is unlikely to affect qualitative results.

In conclusion, these analyses suggest that switching to BAY 81-8973 from rFVIII-FS could result in better protection from bleeds, while enabling patients to remain on the same dosing schedule.

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DISCLOSURES

A. Shah and A. Solms are employees and shareholders of Bayer. S. Lalezari has acted as a consultant on behalf of Bayer, Pi Healthcare, Pfizer, Roche, Takeda and Teva; has attended symposia on behalf of Alnylam, Bayer, Baxter, Biogen, BioMarin, Grifols, Novo Nordisk, Pfizer and Roche; and has attended meetings for Alnylam, Daiichi Sankyo and Janssen. G. Kenet has received research grant support from Alnylam, BPL, Bayer, Baxter, OPKO Biologics and Pfizer; and served on advisory boards and received honoraria for lectures from Alnylam, Bayer, BioMarin, CSL Behring, OPKO Biologics, Pfizer, Shire, Spark and UniQure.

AUTHOR CONTRIBUTIONS

A. Solms was involved in data analysis, writing of the manuscript, and interpretation and discussion of results. G. Kenet was involved in data collection, interpretation of results and critical review of all written study drafts. A. Shah was involved in the design and conduct of the study, data analysis, and interpretation and discussion of results. S. Lalezari was involved in the oversight of the study, data generation and data capture.

Alexander Solms[1]
Shadan Lalezari[2]
Anita Shah[3]
Gili Kenet[2]

[1]*Bayer, Berlin, Germany*
[2]*National Haemophilia Centre, Chaim Sheba Medical Centre, Tel Hashomer, Israel*
[3]*Bayer, Whippany, NJ, USA*

Correspondence
Alexander Solms, Bayer, Berlin, Germany.
Email: alexander.solms@bayer.com

ORCID

Alexander Solms https://orcid.org/0000-0002-0945-2543
Anita Shah https://orcid.org/0000-0002-7846-3115
Gili Kenet https://orcid.org/0000-0003-3494-9823

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