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BAY 81-8973 prophylaxis and pharmacokinetics in haemophilia A: Interim results from the TAURUS study

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Abstract

Objectives: To report interim data from TAURUS, a study assessing real-world prophylactic treatment with unmodified, full-length recombinant FVIII BAY 81-8973 (Kovaltry®; Bayer) indicated for haemophilia A.

Methods: TAURUS (NCT02830477) is an international, open-label, prospective, non-interventional, single-arm study with a one-year observation period (target N = 350). Patients have moderate or severe haemophilia A (FVIII ≤5% or ≤1%) and ≥50 exposure days to any FVIII product. Clinician- and patient-reported outcomes are captured on previous product use, changes in prophylaxis dose and dosing frequency, FVIII consumption, reported bleeding rates, treatment satisfaction and adherence, pharmacokinetic (PK) data (if available) and safety data.

Results: At cut-off, baseline data were available from 160 patients (89 had ≥6 months of follow-up data). Most patients had severe haemophilia A (85%), infused BAY 81-8973 ≥ 3×/wk (59%) and experienced a median number of total bleeds of 2.0 (non-annualised; 246 days median documentation period). Good levels of treatment satisfaction (Hemo-$SAT_{A,P}$) and adherence (VERITAS-Pro) were maintained. TAURUS demonstrated a favourable PK profile of BAY 81-8973 in comparison with other standard half-life rFVIIIs and supported the WAPPS PopPK model. No patients developed inhibitors.

Conclusions: TAURUS data demonstrate effective prophylaxis with BAY 81-8973 in the real world without compromising patient satisfaction or adherence.

KEYWORDS

coagulation disorders, haemophilia, pharmacokinetics, prophylaxis, real-world evidence

1 | INTRODUCTION

Prophylactic treatment with replacement factor VIII (FVIII) is the recommended standard of care for the management of haemophilia A in developed countries. It is a strongly recommended approach in paediatric and adolescent populations, where it has been shown to reduce complications from repeated bleeds, particularly in terms of joint outcomes.[1,2] However, prophylaxis can be costly over the

long term and poor adherence is a common issue. Therefore, improving the cost-effectiveness and convenience of current therapies, or developing new, more affordable solutions, remain high priorities.[2]

BAY 81-8973 (Kovaltry® [octocog alpha]; Bayer) is an unmodified, full-length recombinant FVIII (rFVIII), licensed in 2016 for prophylaxis, perioperative use, and the treatment of bleeds in patients with haemophilia A.[3,4] Approval was based on the safety and efficacy demonstrated in three trials in children and adults in the LEOPOLD clinical development programme.[5-7] In these trials, BAY 81-8973 demonstrated efficacy for the treatment of bleeds, perioperative management and prophylaxis, given as a twice-weekly, three-times-weekly, or every other day (EOD) dosing regimen, where dosing frequency was either decided by the treating physician based on the patient's clinical profile (LEOPOLD I, LEOPOLD Kids) or patients were randomly assigned a high- or low-dose regimen (LEOPOLD II).[5-7] Furthermore, head-to-head cross-over studies with a sucrose-formulated rFVIII (rFVIII-FS; Kogenate® FS; Bayer)[6,8,9] and antihaemophilic factor (recombinant) plasma/albumin-free method (rAHF-PFM; Advate®; Baxter)[10] demonstrated improved pharmacokinetic (PK) and glycosylation profiles for BAY 81-8973,[11] which translate to longer time spent above a FVIII threshold level of 1 IU/dL for typical patients treated with BAY 81-8973. Following its launch in 2016, 13 753 patient-years of exposure to BAY 81-8973 have been estimated up to the 31 August 2018 cut-off.[12] The flexible prophylaxis regimens and dose ranges in the label have the potential to improve convenience for patients and their caregivers, and also to lessen the overall healthcare burden associated with prophylactic treatment, while the higher frequency regimens allow individualised treatment for patients who have a desire to lead a more active life.[3,4] Commonly available FVIII assays can be used to measure FVIII activity with Kovaltry®, and their results have been shown to be comparable to one another.[4,8,13]

The LEOPOLD clinical trials were conducted using strict clinical protocols with clearly defined patient inclusion and exclusion criteria; therefore, the applied treatment schedules and observed efficacy and outcomes may not adequately represent the real-world treatment setting beyond the clinical development programme. Furthermore, there are wide variations in real-world treatment patterns with respect to dosing and frequency of administration arising from differences in prescribing practice and discrepancies between prescribing and patient adherence.[14] Poor characterisation of patient satisfaction with prescribed prophylaxis regimens may also contribute.[14] Therefore, the MulTinational phAse IV study evalUating "Real-world" treatment pattern in previously treated haemophilia A patients Receiving KOVALTRY (octocog alfa) for roUtine prophylaxiS (TAURUS)—an international, open-label, prospective, non-interventional, single-arm study, was conducted to investigate the prophylactic use of BAY 81-8973 and its PK characteristics in standard clinical practice. The full study will run until 2020; however, a scheduled interim analysis (30% patients recruited) was conducted with data collected to 2 July 2018. Here, we present the initial findings of this interim analysis.

2 | PATIENTS AND METHODS

2.1 | Patients

The study included male patients of any age with moderate-to-severe (≤5% FVIII:C) haemophilia A, ≥50 exposure days to any FVIII product, with or without a history of inhibitors, who had been prescribed BAY 81-8973 for a medically appropriate use and who consented to participate. Exclusion criteria were bleeding disorders other than haemophilia A and patients on immune tolerance induction treatment at the time of enrolment.

2.2 | Study design

This phase 4, open-label, uncontrolled, prospective, non-interventional, single-arm study (NCT02830477), with a recruitment period of two years, was conducted in America, Europe and Asia (in countries where BAY 81-8973 has been authorised and is commercially available). Patients were followed up for an observation period of one year, or until the end of their treatment with BAY 81-8973. Patients' clinical data were documented at the time of the initial visit and thereafter during routine clinic visits according to local clinical practice. Additionally, patients recorded data concerning their injections and bleeds in a secure, electronic or paper, bleeding diary and were sent reminders on a monthly basis.

Documented approvals from appropriate independent ethics committees or institutional review boards were obtained for all participating centres before study start. The study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines. Written informed consent was provided by all patients, or their legal representatives before beginning the observations or documentation of any data.

2.3 | Outcomes and assessments

The primary objective of this study was to investigate weekly prophylaxis dosing regimens used in standard clinical practice. Primary outcome measures were the proportion of patients on ≤2× or ≥3× weekly prophylaxis at the end of the observation period, and secondary outcome measures included the number and annualised number of reported bleeds (total, spontaneous, joint and trauma; annualised bleeding values were based on calculations using bleeding data up to the interim cut-off); prophylaxis dosing regimen by age group and country; change in prophylaxis dosing frequency and reason for change (study start to end of observation period); the total annualised factor consumption; physician decision determinants of prophylaxis regimen (the top three reasons from a selection of responses were ranked); occurrence of adverse events (AEs) and serious adverse events (SAEs); and frequency and type of data relating to BAY 81-8973 PK (ie FVIII trough and peak levels, half-life and in vivo recovery) if available. Change in treatment satisfaction from baseline

to end of observation period was assessed using the haemophilia-specific treatment satisfaction questionnaire (Hemo-SAT)[15,16] which has a version for adults (Hemo-SAT_A) and for proxy-rating parents (Hemo-SAT_P), and comprises 34 items pertaining to six dimensions (ease & convenience, efficacy, burden, specialist/nurses, centre/hospital and general satisfaction [total range 0-100; 0 = highest satisfaction]). Change in treatment adherence from baseline to six months and end of observation period was assessed using the self-/parent-reported Validated Haemophilia Regimen Treatment Adherence Scale-Prophylaxis (VERITAS-Pro) which consists of 24 questions on six (four-item) subscales (time, dose, plan, remember, skip and communicate [total range 24-120; 24 = highest adherence]).[17]

Physicians documented an initial visit, follow-up visit(s) and a final visit at 12 months for each patient in an electronic data capture (EDC) system. At the enrolment/initial visit, data on demographics, general medical/surgical history, haemophilia medical and treatment history, bleeding history before study entry, date at initiation of prophylaxis treatment with BAY 81-8973, length of time (over the patient's lifetime) on continuous prophylaxis, details of the most recent FVIII product used, details of previous BAY 81-8973 treatment (if any), prescribed BAY 81-8973 regimen, concomitant medication, physical examination, number of target joints and any BAY 81-8973 PK analysis data (as per routine clinical practice since initiation of BAY 81-8973) were collected by reviewing the patient chart or during the clinical examination.

Follow-up visit(s) were documented as they occurred per routine practice in the EDC system. Data collected during follow-up visits included the following: date of follow-up visit; change in dose and/or dosing frequency of BAY 81-8973 with the reason for change; changes in concomitant medication; physical examination; number of target joints; inhibitor measurement; and AEs.

The final data collection (last visit) was after completion of 12 months of prophylaxis treatment with BAY 81-8973 (one-year observational study period) or at discontinuation of therapy (whichever occurred first). At this final visit, a treatment assessment was conducted, and the patient's condition was documented with additional information on regular end of observation, or discontinuation of observational period with the reason for discontinuation, and reason for product change (if applicable).

2.4 | Pharmacokinetic variables

At baseline and follow-up visits physicians documented FVIII level measurements in addition to known PK parameters (if routinely available at local laboratories). Based on the available FVIII level measurements, individual PK characteristics were estimated via a generic FVIII population PK (popPK) model developed by the www.WAPPS-Hemo.org team at McMaster University.[18] Aggregated summary PK parameters (area under the curve [AUC], terminal half-life [$t_{½term}$], clearance [CL] and time to 1% FVIII level threshold) were calculated.

2.5 | Safety assessments

Data on AEs and SAEs were collected at each visit, starting with the first application of BAY 81-8973 after enrolment into the study and were documented on the AE report form or in the case report form/EDC system. For each AE, the seriousness, duration, relationship to product, action taken and outcome of the event were assessed and documented. In addition, systematic assessments of inhibitor tests were performed and documented, as is usual practice.

2.6 | Statistical analyses

All variables were analysed descriptively with appropriate statistical methods: categorical variables by frequency tables and continuous variables by sample statistics. All analyses were performed for the total study population (overall analysis) and stratified by prophylaxis dosing regimen. Patients who changed regimen during the observation period were included in the analysis of the regimen they were receiving at the data cut-off. An interim analysis was planned when 30% of the total study population was enrolled.

3 | RESULTS

3.1 | Patients

At the time of the interim analysis (data cut-off 2 July 2018), 160 patients had been enrolled from nine countries (Belgium, n = 11; France, n = 13; Germany, n = 38; Netherlands, n = 30; USA, n = 16; Spain, n = 21; Italy, n = 20; Columbia, n = 8; Greece, n = 3) and had analysable data. Before entering the study, the majority of patients had been on prophylaxis (97%). Of these, 83% were on rFVIII-FS.[19]

Baseline demographics and clinical characteristics are shown in Table 1. Overall, 94 (59%) patients were treated with BAY 81-8973 ≥ 3×/wk and 52 (33%) were treated with BAY 81-8973 ≤ 2×/wk (2/52 patients were on 2.5 × weekly prophylaxis [2×/wk to 3×/wk] and have been assigned to the latter group in this analysis); the treatment schedule was missing for 14 (9%) patients (Table 1). Specific BAY 81-8973 regimens for patients who received ≥ 3×/wk dosing at baseline were: daily, n = 2 (1%); 3×/wk, n = 66 (41%); and EOD, n = 26 (16%). BAY 81-8973 regimens for patients who received ≤ 2×/wk dosing at baseline were as follows: 2.5×/wk, n = 2 (1%); 2×/wk, n = 41 (26%); every fourth day, n = 1 (0.6%); 1.5×/wk, n = 1 (0.6%); and 1×/wk, n = 7 (4%). The main reasons for switching to BAY 81-8973 prophylaxis were physician decision (49%), patient decision (16%) and lack of availability of previous FVIII product (13%). Distribution of regimen by age group did not change substantially between baseline and this interim time point; only six adults switched from ≥3×/wk to ≤2×/wk.

3.2 | Reasons for BAY 81-8973 regimen selection

The top three reasons for selection of the initial dose regimen could be ranked from a prespecified list. Overall, the most common reasons ranked first for selecting a particular regimen were "current treatment regimen" (57%), "bleeding history with current treatment regimen" (36%), "patient/caregiver preference" (34%), "adherence/compliance history" (24%) and "activity level" (20%) (Figure 1). "Adherence/compliance history" (indicative of historical adherence/compliance issues) was reported more frequently in the ≤2×/wk group than the ≥3×/wk group (31% vs 23%, respectively). "Parent/caregiver preference" was mentioned more frequently in the ≥3×/wk group than in the ≤2×/wk group (40% vs 33%).

3.3 | Characteristics and bleeding outcomes among patients completing ≥6 months of the observation period

At the cut-off date, 89/160 patients (56%) had completed ≥6 months of the observation period. Of these, at baseline, 29 patients (33%) were treated ≤2×/wk and 60 patients (67%) were treated ≥3×/wk. Most patients had severe haemophilia A (85%), and all were on prophylaxis treatment regimens before the start of the study. Baseline demographics and disease characteristics closely reflected those of the baseline analysis set. Overall, 91% of patients started BAY 81-8973 in the same dosing frequency group as their previous FVIII regimen. Among the 29 patients who received ≤2×/wk at baseline, 28 (97%) continued to receive ≤2×/wk prophylaxis, while one patient (3%) transitioned to a ≥3×/wk schedule. Among the 60 patients who received ≥3×/wk at baseline, 52 (87%) continued to receive ≥3×/wk prophylaxis, while 6 (10%) patients reduced dosing frequency. The proportion of patients on ≤2×/wk increased from 27% (n = 24) prestudy to 33% (n = 29) at baseline and 38% (n = 34) at last follow-up (Figure 2A). The median total weekly prophylactic dose at baseline was 59.5 IU/kg compared with 56.8 IU/kg with previous treatment (Figure 2B).

Patient-reported annualised joint-bleeding rates and annualised spontaneous bleeding rates were low for patients who received ≤2×/wk and ≥ 3×/wk BAY 81-8973 prophylaxis (Table 2); however, it should be noted that at the interim cut-off, most patients had not yet reached one year of observation, and the annualisation of bleeds reported in a shorter time period results in less reliable annualised bleeding rate (ABR) estimates. Therefore, the median reported number of actual total bleeds without annualisation has been provided for reference (Table 2).

3.4 | Patient-reported outcomes among patients completing the observation period

Analysis of VERITAS-Pro and Hemo-SAT$_A$ data among patients with 6 and/or 12 months of data showed similar scores at baseline and follow-up for the ≥3×/wk schedules, indicating high levels of adherence and a good level of treatment satisfaction (Table 3). VERITAS-Pro and Hemo-SAT$_A$ scores showed slightly lower values from baseline to last follow-up with the ≤2×/wk schedule potentially suggesting improved satisfaction and adherence with less frequent dosing (Table 3). A completed Hemo-SAT$_P$ questionnaire at one year after baseline was

TABLE 1 Baseline demographic and clinical characteristics (baseline analysis set)

	≤2×/wk[a] n = 52	≥3×/wk n = 94	Total n = 160[b]
Age (y), median (Q1; Q3)	27.0 (14.0; 42.0)	21.5 (13.0; 35.0)	22.0 (13.0; 40.0)
Length of prestudy prophylaxis (y), median (Q1; Q3)	9.0 (4.0; 15.0)	13.0 (9.0; 19.5)	12.0 (5.5; 17.5)
Patients with >150 exposure days to FVIII, n (%)	47 (90)	86 (92)	142 (89)
Severe haemophilia (FVIII < 1%), n (%)	41 (79)	83 (88)	131 (82)
Patients with at least 1 target joint at baseline, n (%)	21 (40)	35 (37)	60 (38)
Bleeds in 6 mo prestudy[c], median (Q1; Q3)	1.0 (0.0; 2.0)	1.0 (0.0; 2.0)	1.0 (0.0; 2.0)
Joint bleeds in 6 mo prestudy[c], median (Q1; Q3)	0.0 (0.0; 2.0)	0.0 (0.0; 1.0)	0.0 (0.0; 2.0)
Patients with positive inhibitor test, n (%)[d]	2 (3.8)	7 (7.4)	10 (6.3)

Abbreviations: BU, Bethesda units; FVIII, factor VIII; Q1, first quartile; Q3, third quartile.

[a]The 2/52 patients on 2.5×/wk prophylaxis were prescribed a 2×/wk to 3×/wk schedule and were included in the ≤2×/wk group in this analysis. 2.5 represents the answer for "current prophylaxis regimen" for two patients who were prescribed 2-3 times per week.

[b]Dosing schedule information was not available for 14 patients.

[c]Information collected retrospectively by physician.

[d]Median titre for all patients with history of inhibitors was 5.0 BU, and all patients had resolution of last positive inhibitor 13.9 (range, 1.7-21.3) years prior to baseline readings.

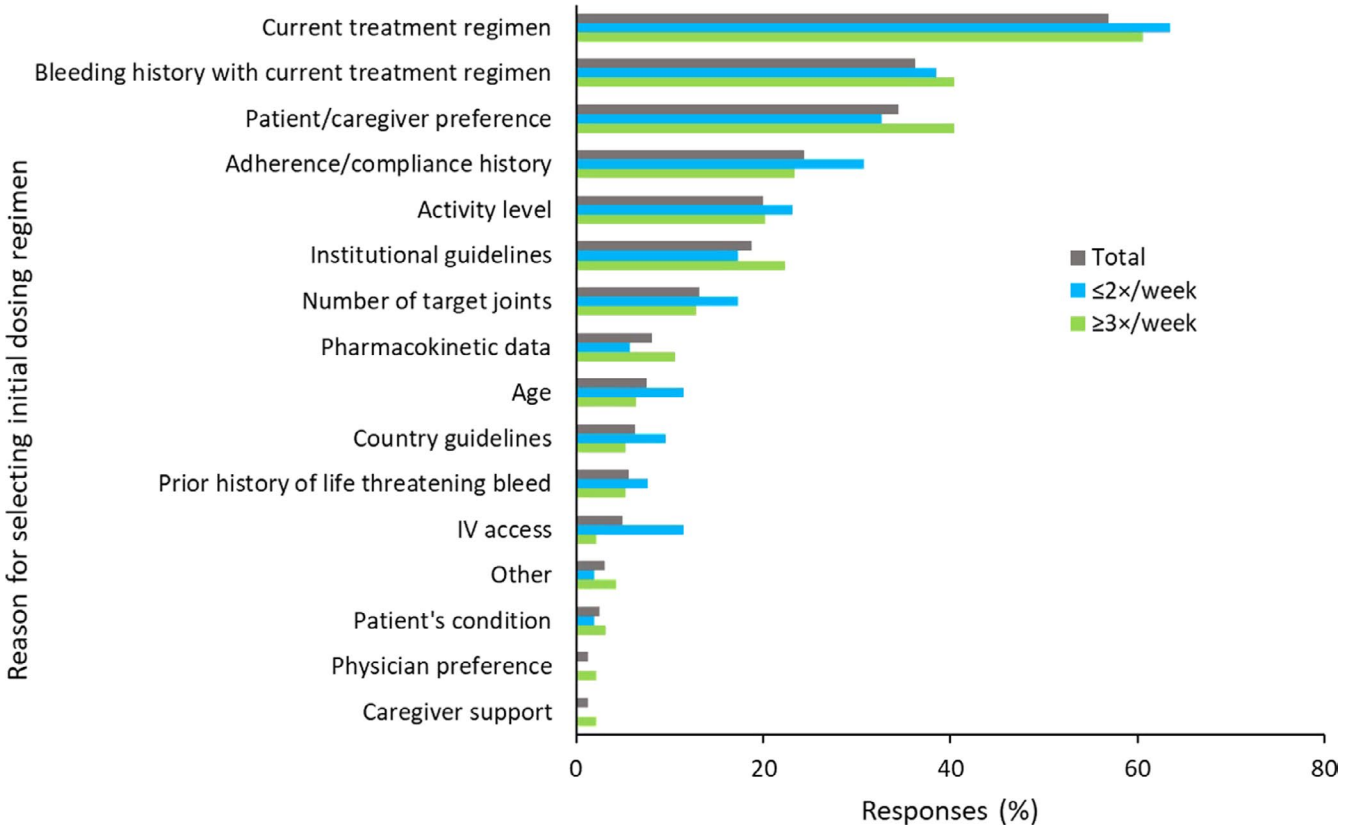

FIGURE 1 Reasons for selecting initial dose regimen. Multiple reasons could be chosen from a predetermined list for selecting the initial dose regimen. ≤2×/wk: 2.5×/wk, 2×/wk, Every 4 d, 1.5×/wk, Every week, Other. ≥3×/wk: Every day, 4×/wk, Every other day, 3×/wk

available for only one patient, and therefore, proxy-reported treatment satisfaction has not been shown in this interim analysis.

3.5 | Safety

Twenty-eight patients (18%) experienced a total of 56 treatment-emergent AEs; the most common Medical Dictionary for Regulatory Activities System Organ Class preferred terms AE categories were injury, poisoning and procedural complications due to accidental traumatic events (5%); most commonly falls and musculoskeletal and connective tissue disorders (7%). Eight patients experienced 10 SAEs, the most common of which was central venous catheter removal (3 of 10 events). One patient with severe haemophilia experienced the only drug-related non-serious AE (pruritus), which resolved following withdrawal of BAY 81-8973; all other AEs were not drug-related. At the time of this interim analysis, no patients had developed FVIII inhibitors according to the systematic documentation of inhibitor assessments performed.

3.6 | Pharmacokinetics

At the cut-off, 59/160 recruited patients with severe (n = 55) or moderate (n = 4) disease (children, n = 18; adults, n = 41; median age [range] 25 [2-64] years) had provided 155 samples for FVIII measurements as part of routine clinical practice (median [range] 2 [1-11] per patient; most subjects either at peak [<1 hour postdose] [54%] or trough [>40 hours postdose] [58%]). The generic WAPPS PopPK model adequately described the individual FVIII data across patients. Parameter plots per age group are shown in Figure 3. Median (5-95% quantiles) of all estimated PK parameters according to the WAPPS PopPK model is also available for two subgroups of patients (<18 and ≥18 years; Table S1). Briefly, median half-life was 11.4 hours and median body weight–normalised clearance was 0.030 dL/h/kg in the <18 years subgroup. Equivalent values in the ≥18 years subgroup were 14.2 hours and 0.026 dL/h/kg, respectively.

4 | DISCUSSION

TAURUS is an ongoing phase 4 study, providing observational data on the prophylactic use of BAY 81-8973 in patients with moderate-to-severe haemophilia A. As BAY 81-8973 is available for use with different regimens, it is important to measure clinical and patient-reported outcomes with these different schedules in a real-world setting.

Examining outcomes such as weekly doses of BAY 81-8973, PK properties, bleeding outcomes, reasons for the initial regimen selection and patient-reported outcomes in an observational study is

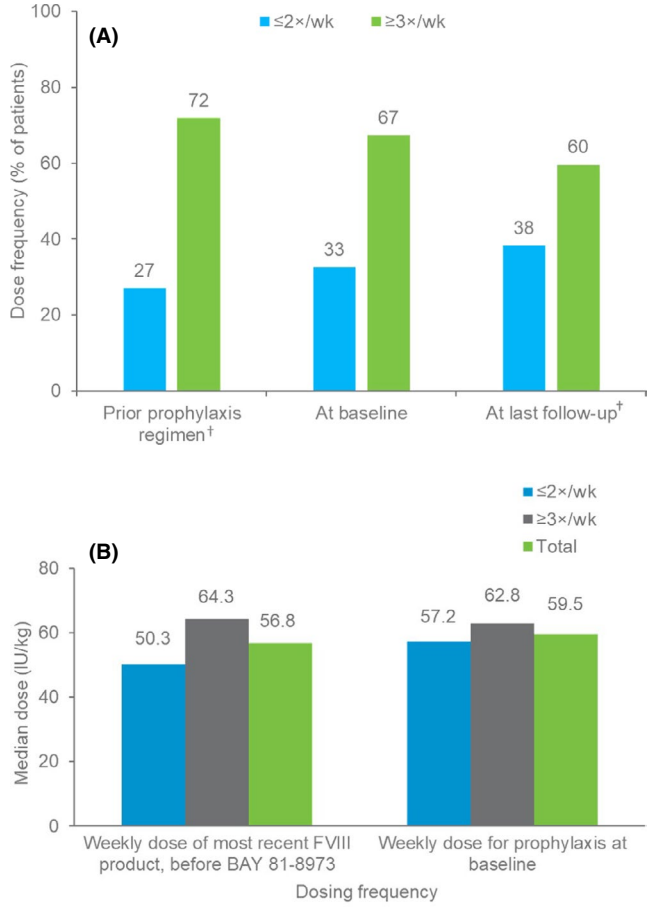

FIGURE 2 (A) Prophylaxis dose frequency of prior FVIII treatment at study baseline and at last follow-up (patients with ≥6 mo of data). †Missing patients, n (%): Prior prophylaxis, 1 (1%); At last follow-up, 2 (2%). (B) Median total dose ≤2×/wk, ≥3×/wk, and total groups before BAY 81-8973 and during weekly prophylaxis (including only patients with ≥6 mo of data). At baseline, median Kovaltry dose per injection for prophylaxis according to treatment schedule was 28.25 IU/kg for the ≤2×/wk subgroup and 23.52 IU/kg for the ≥3×/wk subgroup (both groups combined: 25.76 IU/kg)

particularly important as the populations included in the LEOPOLD clinical trials, in line with clinical trials in general, were tightly controlled and reflect a narrow profile of patients treated with BAY 81-8973 in practice.

Analysis of patient characteristics at baseline revealed that patients who received BAY 81-8973 ≥ 3×/wk were younger and had a longer history of prophylaxis than those treated ≤2×/wk. This indicates successful individualisation of prophylaxis regimen by physicians according to patient characteristics and clinical practice needs. Younger patients may be more likely to receive BAY 81-8973 more frequently for a multitude of reasons, but in general, paediatric patients clear FVIII faster than older patients, resulting in a lower half-life in the former population.[3] In addition, there may be a perceived need for enhanced protection from trauma bleeds in these patients (eg small children who are likely to fall and sustain injury; increased participation in sporting activities). The use of ≤2×/wk regimens in patients with a shorter history of prophylaxis may reflect attempts to manage the disease with a lower frequency schedule at the outset, leaving the potential to transition to a more frequent schedule if required—for example, a "step-up" approach.[20] Interestingly, the most common determinant of BAY 81-8973 regimen choice was current regimen, suggesting an overall tendency for maintaining existing treatment schedules.

These real-world data from the TAURUS study show that after switching to BAY 81-8973, the majority of patients remain on the same individualised prophylaxis treatment regimen for a year postswitch and maintain satisfaction with treatment and good adherence. Studies show a marked variation in treatment adherence among patients with haemophilia, so the findings of good adherence among patients treated with BAY 81-8973 are encouraging.[21-23] Among the small proportion of patients who altered their regimen, the majority moved to a regimen with less frequent dosing, reflecting successful adaptation after the product switch and adding to the body of data that show that BAY 81-8973 treatment can be successfully individualised according to patient need and disease severity. Some patients also successfully continued with higher prophylaxis frequencies, for example EOD regimen (18%).

It is important to emphasise that this is an interim analysis of the TAURUS study and therefore not all patients have been enrolled and/or followed for at least six months. A longer follow-up period in the full population will provide more clinically significant data. Despite the limited sample of 89 patients monitored over a restricted timeframe (≥6 months of treatment), the finding of low bleeding rates confirms and extends the clinical trial results of the LEOPOLD studies,[5-7] demonstrating effective prophylaxis with BAY 81-8973 in routine treatment settings. Interim bleeding rates in TAURUS appear similar to, or lower than, other non-interventional studies with FVIII products such as with rFVIII-FS in Goudier et al (2.8 ± 4.5 total bleeds) and Musso et al (4.8 bleeds per patient on prophylaxis per year).[24,25] However, bleeding rates between studies are difficult to compare as patients with different characteristics and treatment history are included in each study. It would also be inappropriate to directly compare prospective and mainly non-annualised bleeding rate data from the TAURUS study, with annualised data collected retrospectively by physicians for the 6-month period prior to baseline, or in other studies.

TAURUS real-world PK data, captured up to the interim cut-off, support the findings of the previous BAY 81-8973 clinical trials, principally that of the favourable PK profile of BAY 81-8973 in comparison with other standard half-life rFVIIIs. This improved PK profile may translate into clinical benefits for patients switching from a previous FVIII product to BAY 81-8973 prophylaxis, particularly if continuing their dosing regimen.[8,10] The variability in PK parameters observed for both children and adults will be further evaluated in the final TAURUS data set. Nevertheless, TAURUS interim data replicated expected PK differences by age (ie a higher FVIII clearance in children). Furthermore, the WAPPS PopPK model adequately described real-world BAY 81-8973 FVIII activity in 59 patients. The model may facilitate the prediction of PK parameters and enable tailored prophylaxis without the need for extensive sampling.[26]

TABLE 2 Bleeding outcomes prospectively collected in patient-reported bleeding diaries for patients with ≥6 mo of follow-up data

	≤2×/wk (n = 29)	≥3×/wk (n = 60)	All patients (N = 89)
Duration of documentation period (d), median (Q1; Q3)	245.5 (127.0; 337.0)	246.0 (150.0; 347.0)	246.0 (150.0; 344.0)
Number of actual, reported total bleeds, median (Q1; Q3) (non-annualised)	1.5 (0.0; 5.0)	2.0 (0.0; 5.0)	2.0 (0.0; 5.0)
Number of actual reported joint bleeds, median (Q1; Q3) (non-annualised)	1.0 (0.0; 3.0)	1.0 (0.0; 2.0)	1.0 (0.0; 2.0)
ABR, median (Q1; Q3)	2.2 (0.0; 7.7)	4.0 (0.0; 7.5)	3.3 (0.0; 7.5)
AJBR, median (Q1; Q3)	1.4 (0.0; 6.1)	1.1 (0.0; 5.3)	1.1 (0.0; 5.3)

Abbreviations: ABR, annualised bleeding rate; AJBR, annualised joint-bleeding rate; Q1, first quartile; Q3, third quartile.

TABLE 3 Patient-reported outcomes for patients with six months or one year of follow-up data

	≤2×/wk	≥3×/wk	All patients
VERITAS-Pro total score, [n] median (Q1; Q3)			
Baseline	[24] 36.0 (32.0; 45.5)	[47] 36.0 (28.0; 51.0)	[71] 36.0 (31.0; 49.0)
Six months after baseline	[13] 38.0 (32.0; 41.0)	[29] 40.7 (30.0; 50.0)	[42] 39.0 (30.0; 48.7)
One year after baseline	[5] 32.0 (24.0; 34.0)	[15] 36.0 (33.0; 47.0)	[20] 35.5 (31.0; 42.0)
Hemo-SAT$_A$ total score, [n] median (Q1; Q3)			
Baseline	[16] 10.3 (5.1; 20.2)	[30] 13.2 (8.1; 19.1)	[46] 12.9 (7.4; 19.9)
One year after baseline	[3] 8.8 (6.6; 36.8)	[6] 13.6 (11.8; 15.4)	[9] 13.2 (8.8; 15.4)

Note: Hemo-SATA, haemophilia treatment satisfaction questionnaire for adults (total range 0-100; 0 = highest satisfaction); VERITAS-Pro, haemophilia regimen treatment adherence scale (range 24-120; 24 = highest adherence).

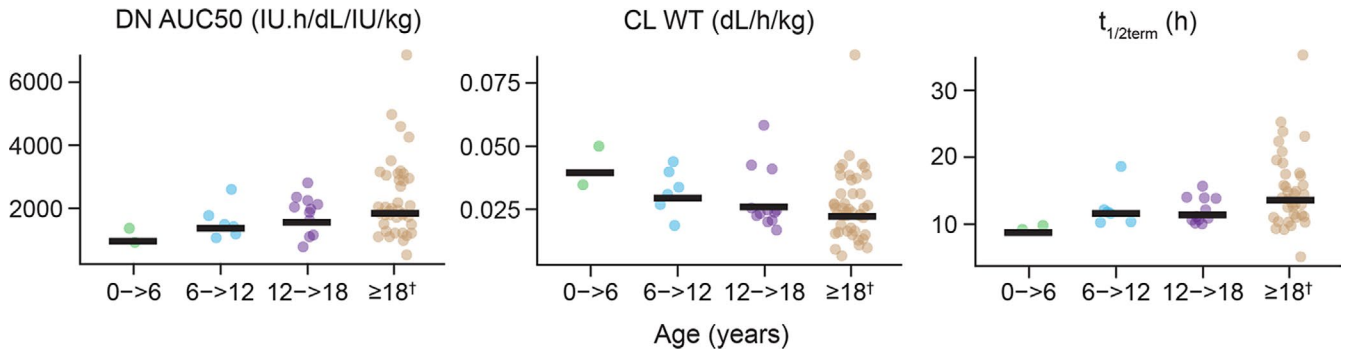

FIGURE 3 PK parameter plots per age group. AUC, area under the curve; AUC50, AUC at which 50% of the maximum therapeutic efficacy is achieved; DN, dose normalised; CL WT, body weight–adjusted clearance; h, hours; IU, international units; $t_{1/2term}$, terminal half-life. †≥18-64 y

Interindividual variance in BAY 81-8973 FVIII activity measurements was observed—which is frequently reported among FVIII products[27]—and could be due to biological factors (eg type of FVIII mutation), or due to methodological or practical differences between local laboratories. As TAURUS is an observational, non-interventional study, laboratory measurements were performed as per routine clinical practice; information on which assays were used is not available, and the type of assay used by a local laboratory could not be instructed by the study sponsor. Of note, however, local laboratories did not report any problems with FVIII activity measurements with BAY 81-8973 during TAURUS up to the interim cut-off.

Overall, these interim data from TAURUS provide an insight into factors determining the choice of treatment schedule with BAY 81-8973, reflect an unproblematic switch from a previous FVIII product to BAY 81-8973, and add to the body of evidence showing that the flexibility of BAY 81-8973 prophylaxis treatment allows different patient needs to be met across a range of disease severities. Confirmation of these findings will be sought at final data analysis following the conclusion of TAURUS in early 2021.

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CONFLICT OF INTEREST

C. Santoro has received honoraria for consulting or lecturing from Amgen, Bayer, CSL Behring, Novartis, Novo Nordisk, Pfizer, Roche, Sobi and Takeda, and speaker's fees from Pfizer, Takeda and Novartis. B. Fuh has received honoraria for consulting or lecturing for Bayer, Micelle Biopharma, Novartis and Pfizer. PQ Le has no disclosures. P. Maes has received grants/research support from Bayer, CSL Behring, Shire, Sobi and Pfizer and honoraria for consulting or lecturing from Bayer, CSL Behring, Novo Nordisk, Pfizer, Shire, Sobi and Roche. R. Berrueco has received grants/research support from Sobi and honoraria for consulting or lecturing from Bayer, CSL Behring, Novartis, Novo Nordisk and Sobi. EM Mingot-Castellano has received honoraria for consulting or lecturing from Amgen, Bayer, Baxter, Novartis, Novo Nordisk Janssen, Roche and Pfizer and speaker's fees from Amgen, Alexion, Bayer, Grifols, Leo Pharma, Novartis, Novo Nordisk, Pfizer, Shire, Sobi and Roche. S. von Mackensen is a consultant for Bayer. A. Solms is an employee and shareholder of Bayer. M. Wang has received honoraria for consulting/advisory from Bayer, Takeda, Novo Nordisk, BioMarin, CSL Behring, Genetech/Roche and Sanofi/Bioverativ.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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