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ORIGINAL ARTICLE

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BAY 81-8973 demonstrated efficacy, safety and joint status improvement in patients with severe haemophilia A in the LEOPOLD I extension for ≤2 years

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Abstract

Objectives: BAY 81-8973 (Kovaltry®), a full-length, unmodified, recombinant human factor VIII, provided excellent bleeding control for patients with haemophilia A in the pivotal 1-year LEOPOLD I trial. The LEOPOLD I extension evaluated long-term efficacy and safety of BAY 81-8973 prophylaxis.

Methods: After completing LEOPOLD I, patients continued receiving 20–50 IU/kg BAY 81-8973 two- or three-times weekly in the extension. Outcomes included annualised bleeding rate (ABR) and haemostasis during surgery.

Results: Fifty-five patients aged 12-65 years participated in the extension. Median (range) exposure days during the 2-year total study period was 309 (115-355). No patient switched regimens. Median (Q1; Q3) ABR for all bleeds was 2.0 (1.0; 6.1) during the pivotal study, 2.0 (0.0; 5.2) during the extension, and 2.0 (0.5; 5.5) combined. The proportion of joint bleeds affecting target joints decreased (pivotal study: 90.9%, extension: 60.0%). Haemostasis was assessed as excellent/good in all five major surgeries. One serious adverse event (myocardial infarction) occurred in a patient with cardiovascular risk factors. No patients developed inhibitors.

Conclusions: BAY 81-8973 prophylaxis efficacy outcomes in the pivotal study were maintained or, in the case of joint protection, improved during the extension, with a safety and tolerability profile consistent with previous experience.

KEYWORDS

clinical trial, haemophilia A, intravenous infusions, recombinant factor VIII, recombinant proteins

1 | INTRODUCTION

Haemophilia A is an inherited blood clotting disorder characterised by low, or absent, factor VIII (FVIII) in plasma, with consequent spontaneous and trauma-induced bleeding, primarily into joints, but also in muscles and other soft tissues.[1] FVIII plasma levels are inversely related to bleeding risk, and patients with trough FVIII levels ≤ 1 IU/dL have a severe disease phenotype characterised by more frequent spontaneous bleeds.[1] The current recommended standard of care for patients with severe haemophilia A is prophylaxis with intravenous injections of FVIII to prevent bleeds and preserve joint structure and function.[1-3]

BAY 81-8973 (Kovaltry®; Bayer, Berkeley, CA, USA) is an unmodified, full-length recombinant human FVIII product approved for routine prophylaxis two- or three-times weekly in adults and children with haemophilia A.[4,5] BAY 81-8973 was first approved in early 2016 in Europe and North America; as of August 2018, more than 867 million IU overall have been administered, with an overall patient exposure of 13,753 patient-years.[6] BAY 81-8973 is manufactured using innovative techniques to eliminate addition of human- and animal-derived raw materials, reduce production steps and enhance pathogen safety; it is produced in a baby hamster kidney (BHK) cell line with the introduction of the chaperone heat shock protein 70 (HSP70).[7] The pharmacokinetics (PK) profile of BAY 81-8973 has demonstrated non-inferiority compared with sucrose-formulated recombinant FVIII (rFVIII-FS; Kogenate FS®; Bayer, Berkeley, CA, USA)[8] and superiority over antihaemophilic factor (recombinant) plasma/albumin-free method (Advate®; Baxalta, Westlake Village, CA, USA) ($t_{1/2}$ 14.5 (25.7) vs 11.7 (27.3) hours, $P < .0001$) [9] in direct-comparison studies of single-dose administration using a crossover design.

The LEOPOLD pivotal clinical trial programme evaluated PK, efficacy, and safety of BAY 81-8973 for routine prophylaxis, treatment of bleeds and perioperative haemostasis in children, adolescents and adults with severe haemophilia A.[10-13] More than 100 million IUs of BAY 81-8973 have been administered as part of the LEOPOLD clinical trial programme. Efficacy and safety of BAY 81-8973 prophylaxis were demonstrated in the multipart 1-year LEOPOLD I trial.[10] In a planned extension phase, patients who completed the pivotal trial were invited to participate in an additional 1-year follow-up study investigating long-term efficacy and safety of BAY 81-8973. The results of this LEOPOLD I extension trial are presented here.

Novelty statements

1. What is the new aspect of your work.
This is the longest pivotal study where efficacy and safety of BAY 81-8973 prophylaxis has been assessed.
2. What is the central finding of your work?
BAY 81-8973 prophylaxis efficacy outcomes were maintained or, in the case of joint protection, improved during the extension, with a safety and tolerability profile consistent with previous experience.
3. What is (or could be) the specific clinical relevance of your work?
This work provides clinicians with data to support the long-term efficacy and safety of BAY 81-8973 prophylaxis two- to three-times weekly in adults.

2 | METHODS

2.1 | Patients

Adult and adolescent patients who completed the efficacy and safety evaluation in the pivotal study (the crossover design of LEOPOLD I, and its inclusion and exclusion criteria have been published previously [10]) were invited to participate in the extension study. Eligible patients, or their parent or legal guardian, provided written informed consent. The protocol was approved by each site's independent ethics committee and/or institutional review board, and the study was conducted in compliance with the Declaration of Helsinki.[14]

2.2 | Study design

The primary objective of the open-label 12-month extension (EudraCT: 2009-012149-43) of the LEOPOLD I pivotal study (NCT01029340) was to assess long-term efficacy and safety of BAY 81-8973 for prophylaxis and for treatment of bleeds in patients with severe haemophilia A. The study was conducted in 20 haemophilia treatment centres from 10 different countries; it began directly following completion of the pivotal study. Potency assignment was determined by chromogenic substrate assay. Patients could elect to continue using their prophylaxis regimen from the pivotal trial (20-50 IU/kg two- or three-times weekly based on investigator discretion, nominal dose as labelled on the vial) or make a single adjustment to dose and/or frequency. BAY 81-8973 was also used to treat breakthrough bleeds at a dose that was dependent on severity and according to physician discretion. Patients who required major or minor surgery during the extension were to be treated with BAY 81-8973.

2.3 | Efficacy and safety assessments

The primary efficacy outcome evaluated during the extension was the annualised bleeding rate (ABR) for all bleeds including joint, spontaneous, trauma-related and untreated bleeds, as well as for injections reported for the purpose of "other" (assumed to be for a bleed or before a procedure). Additional efficacy outcomes were bleeds which occurred within 48 h after a prophylaxis infusion, ABRs for different bleed types, the percentage of target joint bleeds, FVIII consumption, number of injections required to treat bleeds, patient assessment of treatment response (excellent, good, moderate or poor) and health-related quality of life (HRQoL). Patients completed the Haemo-QoL (for ages < 18 years) or Haemo-QoL-A (for ages ≥ 18 years), a haemophilia-specific HRQoL questionnaire, at the end of the pivotal study (start of extension) and at month 12 of the extension. Haemostatic outcomes for major or minor surgeries included blood loss, need for transfusion and haemostasis-related surgical complications.

Safety outcomes included FVIII inhibitor development, formation of antibodies against HSP70 or BHK cell proteins, and adverse events (AEs). Regimen adherence, bleeding events and response to bleed treatment were recorded in electronic patient diaries

and reviewed by investigators in addition to clinical observations. Patients attended five site visits (at extension start and months 3, 6, 9 and 12) during the extension, at which treatment adherence and AEs were reviewed. Inhibitors against FVIII (Nijmegen-Bethesda assay) were evaluated at first visit, after 6 months and at final visit. Routine laboratory parameters and antibodies against HSP70 and BHK/host cell protein (HCP) were evaluated at extension start and final visit.

2.4 | Statistical analysis

The patient sample size from the pivotal study was consistent with regulatory requirements of the European Medicines Evaluation Agency. Safety was planned to be evaluated in participants who received ≥ 1 dose of BAY 81-8973 in the extension study. Efficacy was planned to be evaluated in the intent-to-treat (ITT) population, which included patients with available information regarding bleeds. A responder analysis was performed, with response rates defined by ABR for joint bleeds (joint ABR ≤ 1; joint ABR > 1 to ≤ 4; joint ABR > 4). Summary statistics and frequencies were calculated using SAS version 9.2 (SAS Institute Inc, Cary, NC, USA).

3 | RESULTS

3.1 | Patients

Of 61 patients who completed the pivotal study, 55 patients aged 12 to 61 years (median age at start of pivotal study, 31 years) entered the extension phase and were included in the safety and ITT populations. Of these, 43 patients (78.2%) continued in the extension for the entire 1-year duration, and 12 patients (21.8%) discontinued because of participation in another study (n = 8), AEs (n = 1), withdrawn consent (n = 1), planned surgery and investigator decision to withdraw patient (n = 1), or non-compliance (n = 1). No patients switched dosing frequency between the pivotal study and extension, and no patients were lost to follow-up during the extension. Demographic and baseline disease characteristics for all extension participants reported at the start of the pivotal study are summarised in Table 1; baseline characteristics overall were similar between groups receiving twice weekly and three-times weekly prophylaxis. However, compared with two-times weekly patients, three-times weekly patients were younger, more likely to have ≥ 1 target joint, had experienced more bleeds in the 12 months before pivotal study enrolment, and were less likely to have previously

TABLE 1 Demographics and baseline characteristics for patients in the extension[a]

	Patients with 2x/wk dosing (n = 17)	Patients with 3x/wk dosing (n = 38)	Total patients (N = 55)
Age, y			
Median (range)	39.0 (12-61)	30.0 (12-60)	31.0 (12-61)
Age group, n (%)			
12-17 y	3 (17.6)	5 (13.2)	8 (14.5)
18-29 y	3 (17.6)	13 (34.2)	16 (29.1)
30-59 y	10 (58.8)	19 (50.0)	29 (52.7)
60-64 y	1 (5.9)	1 (2.6)	2 (3.6)
Race, n (%)			
White	17 (100.0)	33 (86.8)	50 (90.9)
Black	0	3 (7.9)	3 (5.5)
Hispanic	0	2 (5.3)	2 (3.6)
BMI, kg/m^2			
Median (range)	26.1 (16.7-31.4)	25.2 (16.2-33.1)	25.4 (16.2-33.1)
Previous treatment, n (%)			
Prophylaxis	15 (88.2)	29 (76.3)	44 (80.0)
On demand	2 (11.8)	9 (23.7)	11 (20.0)
Patients with target joints, n (%)	9 (52.9)	31 (81.6)	40 (72.7)
Median (range) bleeds in the previous 12 mo	4.0 (0-37)	8.0 (0-55)	6.0 (0-55)
Median (range) joint bleeds in the previous 12 mo	3.0 (0-35)	5.0 (0-55)	4.0 (0-55)

Abbreviation: BMI, body mass index.

[a]These values reflect baseline characteristics reported at the beginning of the pivotal LEOPOLD I trial.

used prophylaxis (Table 1). Across both dosing regimens combined, 72.7% of patients had ≥ 1 target joint, and there was high variability among the number of bleeds within 12 months before pivotal study enrolment (range, 0-55). Median (range) number of bleeds during this same 12-month period was 36.0 (0-55) for patients previously treated on demand (20% of patients) and 4.0 (0-40) for patients previously treated with prophylaxis (80% of patients). Median Gilbert total score at baseline of the pivotal study for all patients who continued in the extension was 20.0 (range, 0-51; maximum total score is 100 points, with 0 reflecting normal, unaffected joints); median Gilbert score was 2.0 for both the pain and bleeding subscales and 13.5 for the total score excluding pain and bleeding (maximum total score excluding subscales is 62 points).

3.2 | Treatment exposure

The 55 extension study participants had a median (range) of 154 (10-192) exposure days (EDs) during the 366 days spent in the extension study. The median (range) nominal dose used by all patients to treat bleeds was 34.2 (15.5-67.5) IU/kg/infusion and 23 of the 154 bleeds (14.9%) treated during the extension were rated by patients as severe. The extent of exposure during the pivotal and extension trials has been summarised in Table 2.

3.3 | Efficacy

The median ABR (quartile [Q]1; Q3) for all bleeds was 2.0 (1.0; 6.1), 2.0 (0; 5.2) and 2.0 (0.5; 5.5) for the pivotal phase, extension phase and the two study phases combined, respectively (Table 3). The percentage of patients with 0 bleeds was 23.6% during the pivotal study and 32.7% during the extension. There was a trend towards a decrease in the proportion of spontaneous bleeds (64.9% during the pivotal study vs 52.7% during the extension, reflecting better protection; median ABR for trauma-related bleeds was 0 for the pivotal study, extension, and both study phases combined). The median (Q1; Q2) number of bleeds within 48 h after replacement in the pivotal study was 1 (0; 3) and this remained the same in the extension.

Responder rates in the extension, defined by joint-bleed ABR, are shown in Table 4. During the extension, among all patients, 26 (47.3%) had a joint ABR ≤ 1, 17 (30.9%) had a joint ABR > 1 to ≤ 4, and 12 (21.8%) had a joint ABR > 4. For adults (aged ≥ 18 years, n = 47), the numbers were 22 (46.8%), 15 (31.9%) and 10 (21.3%), respectively; for adolescents (aged 12 to < 18 years, n = 8), the numbers were 4 (50.0%), 2 (25.0%) and 2 (25.0%), respectively. There were some differences in clinical characteristics for patients with a joint ABR ≤ 1 compared with individuals with higher joint ABR. For example, compared with those with joint ABR ≤ 1, patients with joint ABR > 4 were more likely to be treated twice-weekly during the study, had a higher total Gilbert score at main study baseline, and experienced a higher median number of all bleeds and joint bleeds in the 12 months prior to the main study (Table 4).

Improved joint protection was also demonstrated by the decrease in the proportion of joint bleeds affecting target joints, which was 90.9% (range 0-100) in the pivotal study compared with 60% (range 0-100) in the extension (Table 4).

The median number of days before the first bleeding episode occurred increased from 39.5 during the pivotal study to 82.3 during the extension, showing improved bleeding control overall. Adherence to prophylaxis regimen was high (≥90%) for all patients during the pivotal period and for 54/55 patients (98.2%) during the extension.

The median number of infusions required to treat bleeds was 1 (range, 0-48) for the pivotal study alone and for the pivotal study combined with the extension phase. For the extension phase alone, the median number of infusions required to treat bleeds was 1

TABLE 2 Extent of exposure per subject in pivotal and extension trial

	Pivotal study (N = 55)	Extension study (N = 55)	Combined (N = 55)
Number of days in period, median [min;max]	364 [348;376]	366 [22;377]	730 [386;749]
Exposure days in period, median [min;max]	157 [105;178]	154 [10;192]	309 [115;355]
Nominal dose used to treat bleeds, median (range), IU/kg/infusion	28.6 (12.9-54.3)	34.2 (15.4-67.4)	32. 7 (13.5-67.4)
Nominal dose per prophylaxis infusion of BAY 81-8973, median (range), IU/kg/infusion			
2x/wk dosing	34.3(20.6-41.9)	29.3 (17.5-43.3)	33.6 (19.1-42.5)
3/wk dosing	30.9 (24.2-43.4)	30.7 (23.5-44.6)	30.9 (24.0-44.0)
Nominal total BAY 81-8973 consumption, median (range), IU			
Prophylaxis	329 260 (111 662-584 434)	314 000 (9000-570 000)	637 210 (217 662-1 154 434)
All infusions	349 013.0 (115 288-592 093)	336 500 (22 000-837 000)	681 331 (223 288-1 317 611)
Nominal total consumption per year, median (range), IU/kg/y			
2x/wk dosing	3650.74 (2199.1-5037)	3634.52 (1862.3-5096.8)	3732 (2047-5067)
3x/wk dosing	5082.6 (4064.4-7785.6)	4913.36 (3702.1-12 497)	4996 (3942-8121)

Abbreviations: Max, maximum; Min, minimum.

(range 0-28). Across all study phases, 329 of 386 bleeds (85.2%) were treated with ≤ 2 infusions. Eight bleeds (2.1%) did not require additional treatment other than regular prophylaxis. Patients reported a good or excellent response to treatment in 77.4% of cases.

Five major surgeries were performed during the extension. Haemostasis was assessed by the surgeon as excellent or good in all cases, and only one procedure (compartment syndrome splitting) was considered emergent surgery. Additionally, one patient within the extension received a blood transfusion during surgery.

3.4 | Health-related quality of life

Good HRQoL at baseline in this patient population, most of whom were receiving prophylaxis before the study, was maintained during the first and second year of treatment. Median Haemo-QoL-A transformed total score in adults was 78.1 points at baseline (maximum score is 100 points, indicating best possible HRQoL) and was maintained (median change, <0.1 points) up to the end of the extension (median, 79.8 at end of year 1 and 79.0 at end of extension).

3.5 | Safety

In total, 37 patients experienced 88 AEs (67.3%) during the extension. Most events were mild or moderate, and only four events in 3 patients were considered potentially related to the study drug (seasonal allergy, two instances of pruritus in 1 patient and myocardial infarction). There were 13 serious AEs (SAEs) reported in 8 patients. In 1 patient aged 62 years with known multiple cardiovascular risk factors, one SAE (myocardial infarction) occurred for which a causal relationship with BAY 81-8973 could not be excluded. The event led to hospitalisation and study discontinuation but was resolved by the end of the extension, as reported previously.[10]

No patients developed antibodies against FVIII or anti BHK/HCP antibodies during the extension. Before entry in LEOPOLD I and

TABLE 3 Summary of bleeds in the pivotal study and extension

	Pivotal study	Extension	Pivotal study + extension
	Year 1 (N = 55)	Year 2 (N = 55)	Years 1 and 2 (N = 55)
All bleeds/y[a]			
Median (Q1; Q3)	2.0 (1.0; 6.1)	2.0 (0.0; 5.2)	2.0 (0.5; 5.5)
Mean ± SD	4.2 ± 5.4	3.7 ± 5.0	3.8 ± 4.6
2-times weekly dosing group[b]			
Median (Q1; Q3)	1.02 (0.0; 8.03)	2.01 (0.0; 6.9)	1.98 (0.5; 5.5)
Mean ± SD	5.1 ± 7.7	4.3 ± 5.2	4.5 ± 6.3
3-times weekly dosing group[b]			
Median (Q1; Q3)	3.0 (1.0; 6.0)	1.9 (0.0; 4.9)	2.5 (0.5; 5.5)
Mean ± SD	3.8 ± 4.1	3.5 ± 4.9	3.5 ± 3.6
Joint bleeds/y			
Median (Q1; Q3)	1.1 (0.0; 4.1)	1.0 (0.0; 3.9)	1.5 (0.5; 4.0)
Mean ± SD	3.3 ± 4.9	2.7 ± 3.9	3.0 ± 4.1
Spontaneous bleeds/y			
Median (Q1; Q3)	1.0 (0.0; 4.0)	1.0 (0.0; 2.0)	1.0 (0.5; 3.3)
Mean ± SD	2.7 ± 3.6	1.8 ± 3.0	2.3 ± 3.1
Trauma bleeds/y	0.0 (0.0; 1.0)	0.0 (0.0; 1.2)	0.0 (0.0; 1.3)
Median (Q1; Q3)	1.4 ± 3.8	1.8 ± 3.7	1.4 ± 3.2
Patients with 0 bleeds, n (%)	13 (23.6)	18 (32.7)	9 (16.4)
Joint bleeds within target joints, n (% of joint bleeds[c] which were within target joints)			
2x/wk dosing	11 (84.6)	5 (45.5)	16 (66.7)
3/wk dosing	70 (70.0)	48 (63.2)	118 (67.0)

Abbreviations: Q, quartile; SD, standard deviation.

[a]"All bleeds" refers to all treated or untreated spontaneous or trauma-related bleeds, as well as bleeds with a missing reason and four infusions reported for the purpose of "other."

[b]n = 17 for 2x/wk dosing group, n = 38 for 3x/wk dosing group.

[c]In patients with target joints at baseline and having joint bleeds throughout the period.

TABLE 4 Responder rates by treatment frequency and clinical characteristics

	Responder rate		
	Joint ABR ≤ 1 (n = 26)	Joint ABR > 1–≤4 (n = 17)	Joint ABR > 4 (n = 12)
Treatment frequency, n (%)			
2×/wk	7 (26.9)	5 (29.4)	5 (41.7)
3×/wk	19 (73.1)	12 (70.6)	7 (58.7)
Baseline[a] Gilbert score, median (range)[b]			
Pain	2.0 (0-8)	2.0 (0-18)	1.0 (0-8)
Bleeding	2.0 (0-9)	4.0 (0-12)	2.0 (0-11)
Total	18.5 (0-43)	19.0 (5-51)	21.5 (3-41)
Total excluding pain and bleeding	12.0 (0-35)	15.0 (0-38)	18.0 (1-32)
Target joints present at baseline[a]			
No	7 (26.9)	5 (29.4)	3 (25.0)
Yes	19 (73.1)	12 (70.6)	9 (75.0)
Number of bleeds in past 12 mo prior to the study[a], median (range)	4.0 (0-55)	9.0 (0-50)	9.0 (0-40)
Number of joint bleeds in past 12 mo prior to the study[a], median (range)	2.0 (0-55)	5.0 (0-15)	5.5 (0-40)

Abbreviation: ABR, annualised bleeding rate.

[a]These values reflect baseline characteristics reported at the beginning of the pivotal LEOPOLD I trial.

[b]Higher scores indicate worsening outcomes.[25]

treatment with BAY 81-8973, most patients had detectable levels of anti-HSP70 antibodies that were below 239 ng/mL, the cut-off value at which patients were considered positive for anti-HSP70-antibodies.[15] Antibodies against HSP70 were detected in 1 patient during the extension, and another patient who had developed anti-HSP70 antibodies during the pivotal study remained slightly above the threshold for positivity throughout the extension. For both patients, positive anti-HSP70 antibody levels coincided with AEs involving inflammation (infection and arthritic pain). However, no definitive clinical sequelae were observed in association with the positive antibody levels, and neither patient experienced an AE deemed treatment-related by the investigator.

4 | DISCUSSION

This LEOPOLD I trial extension demonstrated that BAY 81-8973 was efficacious and well tolerated as twice weekly or three-times weekly prophylaxis for up to 2 years of treatment in patients in whom prophylaxis dose and frequency was assigned by the investigators. Patients assigned to three-times-weekly dosing were generally younger than those receiving twice weekly dosing, had a higher number of bleeding episodes before the study, and were more likely to have target joints and to have previously been treated on demand. These differences in patient characteristics indicate that investigators selected prophylaxis regimens according to the individual patient's clinical characteristics and treatment needs.

The number of bleeds was consistently low, with median ABRs of 2.0 for all bleeds and 1.0 for spontaneous bleeds. Responder rates during the extension were high: joint ABRs were ≤ 1 for nearly 50% of patients, >1 to ≤ 4 for 30%, and > 4 for only 20%.

The subset of patients who received prophylaxis twice weekly also had low median ABRs during the pivotal study[10] and extension, with bleeding rates and characteristics similar to those observed in three-times weekly patients and the study population overall. Of note, improved joint protection with BAY 81-8973 treatment was demonstrated by decreased proportions of spontaneous bleeds and the proportion of joint bleeding episodes affecting target joints, from 90.9% during the pivotal study to 60.0% during the extension. Given that 72.7% of patients had target joints at baseline, these results indicate that BAY 81-8973 prophylaxis is efficacious in patients who have experienced multiple prior bleeding episodes. Good HRQoL at baseline in these patients, most of whom were being treated with prophylaxis before the study, was maintained until study end.

In general, patient outcomes remained stable or improved during the extension compared with the pivotal study. The percentage of patients with 0 bleeds was 23.6% during the pivotal trial and 32.7% during the extension, and 9 patients (16.4%) remained bleed-free throughout the entire 2 years.

BAY 81-8973 was also efficacious for the treatment of bleeds. Over the course of the 2 years, 87.3% of bleeds were treated with two or fewer infusions, and response to treatment was good or excellent for 77.4% of treated bleeds. One study centre reported the use of 48 infusions due to a local protocol to routinely continue treatment until all symptoms were resolved.

Similar to observations during the pivotal study, BAY 81-8973 was generally well tolerated, with only 3 patients experiencing AEs that were possibly related to treatment. The majority of all AEs were mild or moderate in severity. One treatment-related AE, an acute myocardial infarction in a 62-year-old patient with known risk factors for cardiovascular events (including smoking, hypertension, hyperlipidaemia and coronary arteriosclerosis), was classified as an SAE and led to study discontinuation; details were provided previously in the brief extension study section of the report of LEOPOLD I pivotal trial results.[10] This was also consistent with an age-related risk of cardiovascular complications in patients with haemophilia.[16] The occurrence of this particular event may suggest that older patients with cardiovascular risk factors could potentially benefit from regimens that include more frequent weekly infusions with a low dose of FVIII per infusion. Patients with haemophilia may have the same risk of cardiovascular events

as those without haemophilia when clotting has been normalised by treatment with FVIII.[17] Increases in FVIII levels after infusion of a FVIII product, particularly in a patient with existing cardiovascular risk factors, might put the patient at the same risk for vessel closure or myocardial infarction as a person without haemophilia.[18-20] Consequently, patients with haemophilia receiving FVIII prophylaxis should be evaluated for cardiac risk factors.[21-24]

None of the patients developed neutralising antibodies against FVIII or antibodies against BHK/HCP. Most patients had detectable levels of anti-HSP70 antibodies before BAY 81-8973 treatment that were below the cut-off for positivity.[15] Low-titre antibodies against HSP70 were detected in only 2 patients during the extension, both of whom had concurrent AEs involving inflammation; both patients maintained good bleeding control with no clinical symptoms that were determined to be treatment-related.

One important limitation of this study was the subjective evaluation of bleeds, which were quantified based on electronic patient diary entries and classified according to patient assessment. Additionally, results should be interpreted with the consideration that this was an extension study of a non-randomised, open-label clinical trial and included a moderate number of patients (n = 55).

5 | CONCLUSIONS

BAY 81-8973 was efficacious in preventing and treating bleeds for the entire 2-year study duration of the LEOPOLD I pivotal study and extension, with low bleeding rates observed throughout the first and second years of treatment, and a safety and tolerability profile consistent with previous experience. Over the course of 2 years, bleeding rates, severity and characteristics either remained stable or improved, with a decrease in spontaneous bleeds observed over time, and a decrease in the proportion of joint bleeding episodes affecting target joints, indicating improved joint protection compared to the pivotal study, and confirming the suitability of BAY 81-8973 for long-term treatment.

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D. Tseneklidou-Stoeter, H. Beckmann and N. Church are employees of Bayer. H. Beckmann also has shares in Bayer.

AUTHOR CONTRIBUTIONS

J. Mahlangu: data collection, analysis and interpretation of data. M. F. Lopez Fernandez: data collection, analysis and interpretation of data. E. Santagostino: data collection, analysis and interpretation of data. S. Lalezari: data collection, analysis and interpretation of data. D. Tseneklidou-Stoeter: analysis and interpretation of data. H. Beckmann: analysis and interpretation of data. N. Church: analysis and interpretation of data. Contribution to study conception/design or data acquisition/analysis or interpretation: all authors. Manuscript drafting/revision: all authors. Final approval of submitted draft: all authors. Agreement to be accountable for all aspects of the work: all authors.

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