

CLINICAL PHARMACOLOGY BLA REVIEW

Division of Hematology
Office of Blood Review & Research

BLA 125574/0

CBER Date Received: December 16, 2014

Product: Antihemophilic Factor (Recombinant)

Sponsor: Bayer Corporation

Indication: Treatment of Hemophilia A

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Through: Bindu George, M.D.

Introduction/Background

Coagulation factor FVIII is a normal constituent of human plasma and is predominantly produced in the liver and if not utilized within coagulation events degraded by the mononuclear phagocyte system. FVIII circulates in the plasma non-covalently bound to VWF.

Hemophilia A is an inherited sex-linked disorder of blood coagulation in which affected males do not produce functional coagulation FVIII in sufficient quantities to achieve satisfactory hemostasis. The incidence of congenital hemophilia A is approximately 1 in 10,000 births. Disease severity is classified according to the level of FVIII activity (% of normal) as mild (>5% to <40%), moderate (1% to 5%) or severe (<1%). Due to deficiencies in FVIII, patients with hemophilia A are predisposed to recurrent bleeding episodes (BEs). Most BEs occur in joints and muscles. Without adequate treatment these repeated hemarthroses and hematomas lead to long-term sequelae with severe disability. The optimal effective treatment of this bleeding disorder is replacement of FVIII using FVIII concentrate either obtained by fractionation of human plasma (pFVIII) or manufactured by recombinant DNA technology (rFVIII).

Bayer has developed a full-length recombinant human coagulation factor VIII (rFVIII) product (BAY 81-8973), formulated with sucrose. BAY 81-8973 is supplied lyophilized in sterile glass vials and is reconstituted with sterile water for injection. It will be available in five vial sizes (250 International Units [IU], 500 IU, 1000 IU, 2000 IU and 3000 IU per chromogenic substrate assay). The rFVIII protein BAY 81-8973 is essentially identical to the currently marketed product Kogenate FS. The rFVIII protein concentration and the composition of the excipients are the same as in Kogenate FS. Compared to Kogenate FS, BAY 81-8973 is produced with a new cell bank, which includes the gene for human heat shock protein 70 (HSP70), and other improvements in the production processes. In addition, all animal- and human-derived additives have been eliminated from the cell culture and purification processes and a virus filtration step has been introduced for improved non-enveloped viral clearance robustness.

The company is seeking approval in the U.S. for the following indications in adults and children diagnosed with hemophilia A:

- Routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes
- Control and prevention of bleeding episodes
- Peri-operative management (surgical prophylaxis)

The clinical pharmacology of BAY 81-8973 has been assessed in 3 submitted studies. The studies Leopold 1, Leopold 2, and Leopold Kids include a full analysis of PK parameters. However, in studies Leopold 2 and Leopold Kids participation in PK was optional. An additional submitted Population PK report is not included in this review, because the regulatory assessment of adequacy of study design, PK results, and conclusions is based on the original submitted study reports.

1. Study Title: A two-part, randomized, cross-over, open-label trial to evaluate the pharmacokinetics, efficacy, and safety profile of plasma protein-free recombinant FVIII formulated with sucrose (BAY 81-8973) in previously treated subjects with severe hemophilia A under prophylaxis therapy. Report No. A62366 (“Leopold 1”)

2. Study Title: A phase II/III, randomized, cross-over, open-label trial to demonstrate superiority of prophylaxis over on-demand therapy in previously treated subjects with severe hemophilia A treated with plasma protein-free recombinant FVIII formulated with sucrose (BAY 81-8973). Report No. PH-37042 (“Leopold 2”)

3. Study Title: A multi-center Phase III uncontrolled open-label trial to evaluate safety and efficacy of BAY 81-8973 in children with severe hemophilia A under prophylaxis therapy. Report No. A51496 (“Leopold Kids”)

1. Study Title: A two-part, randomized, cross-over, open-label trial to evaluate the pharmacokinetics, efficacy, and safety profile of plasma protein-free recombinant FVIII formulated with sucrose (BAY 81-8973) in previously treated subjects with severe hemophilia A under prophylaxis therapy. Report No. A62366 (Leopold 1)

Study objectives

Part A (Phase I)

Primary objective:

- To demonstrate the pharmacokinetic non-inferiority of BAY 81-8973 as compared to Kogenate FS using bioequivalence criteria following single dose administration.

Secondary objective:

- To evaluate the *in vivo* recovery of FVIII plasma levels 15 minutes post single injection of BAY 81-8973.

Part B (Phase II-III)

Primary objective:

- To demonstrate the efficacy and safety of BAY 81-8973 for the treatment of bleeds and prophylaxis.

Secondary objectives (Clinical Pharmacology relevant):

- To compare *in vivo* recovery at the 6 month periods based on potency determinations (CS/EP versus CS/ADJ) during prophylactic treatment with BAY 81-8973.
- To evaluate the potential for inhibitory antibody formation during prophylactic treatment with BAY 81-8973.
- To evaluate the potential for antibody formation to HSP-70 and/or hamster proteins during prophylactic treatment with BAY 81-8973.

Part C (Phase II-III)

- To evaluate surgical outcomes in ≥ 15 anticipated surgeries in ≥ 15 subjects across both studies (Protocol 12954 and Protocol 14319) treatment with BAY 81-8973.

Overall Study Design

Leopold I was composed of 3 parts (A, B, C) and an optional extension phase. Primary objective of Part A was to assess the PK non-inferiority of BAY 81-8973 compared to Kogenate FS in subjects with severe hemophilia A. The potency of the BAY 81-8973 drug product vials used for both products was determined by the chromogenic substrate assay (CS) per European Pharmacopoeia (CS/EP). Part B assessed the safety, tolerability, and efficacy of prophylaxis treatment with BAY 81-8973 in subjects with severe hemophilia A over a 12 month treatment period. Only those subjects who participated in Part A were re-tested for BAY 81-8973 PK after 6 or 12 months of treatment in Part B. Part C was dedicated to major surgery only. The extension part was an optional continuation of the prophylaxis treatment for up to 12 additional months.

PK data were obtained in a randomized cross over study following a single dose of 50 IU/kg of BAY 81-8973 or Kogenate FS in 26 patients between the ages of 12 to 61 years with severe hemophilia A. The washout period between the 2 treatments was ≥ 3 days. Repeat PK were also obtained in 19 patients using a dose of 50 IU/kg BAY 81-8973 after 6 or 12 months of prophylaxis treatment.

For all PK evaluations, 50 IU/kg of BAY 81-8973 or Kogenate FS was given as an IV-infusion over 10 min. Blood samples were collected at pre-injection, and at 0.25, 0.5, 1, 3, 6, 8, 24, 30, and 48 hours following the injection.

Analytical assay and data analysis software:

FVIII plasma activity was determined by the one-stage clotting assay (OC) (LLOQ = 1 IU/dL) and the chromogenic assay (CS) (LLOQ = 3 IU/dL) in a central lab. For all PK evaluations, the potency assignment of BAY 81-8973 as well as of the comparator Kogenate FS was determined by CS/EP. PK parameters were calculated using the model-independent (non-compartment) method (b) (4) in conjunction with the (b) (4)

Results:

Table 1 (OC assay) and Table 2 (CS assay) summarize the results for the PK analysis in study Leopold I (Part A). The ratio of both drugs (BAY 81-8973 / Kogenate FS) and the corresponding 90% CIs were calculated for AUC and Cmax to evaluate the non-inferiority of BAY 81-8973 compared to Kogenate FS. Using data from the OC and the CS assays, both analyses showed that the bioavailability of BAY 81-8973 was at least non-inferior to that of Kogenate FS. With both assays, the 90% CIs for the ratio 'BAY 81-8973 / Kogenate FS' of Cmax were within the bioequivalence criteria of 0.80 to 1.25. For AUC, the 90% CIs for the ratio 'BAY 81-8973 / Kogenate FS' were 1.13 to 1.25 (OC assay) and within 1.11 and 1.28 (CS assay). Overall, the rFVIII potency data demonstrated PK non-inferiority for BAY 81-8973 compared to Kogenate FS.

Based on the OC assay a direct comparison of the relevant PK parameters are shown as follows (arithmetic mean \pm SD). BAY 81-9073 for adults (≥ 18 yr): systemic clearance CL = 0.035 ± 0.012 dL/h/kg, terminal half-life $t_{1/2}$ = 14.3 ± 3.7 h; and for adolescent (12-17 yr): systemic clearance CL = 0.053 ± 0.017 dL/h/kg, terminal half-life $t_{1/2}$ = 11.7 ± 1.11 h. Kogenate FS for adults (≥ 18 yr): systemic clearance CL = 0.043 ± 0.017 dL/h/kg, terminal half-life $t_{1/2}$ = 12.9 ± 3.1 h; and for adolescent (12-17 yr): systemic clearance CL = 0.056 ± 0.016 dL/h/kg, terminal half-life $t_{1/2}$ = 11.1 ± 2.6 h.

Based on the CS assay results are shown as follows (arithmetic mean \pm SD). BAY 81-9073 for adults (≥ 18 yr): systemic clearance CL = 0.027 ± 0.01 dL/h/kg, terminal half-life $t_{1/2}$ = 14.2 ± 3.5 h; and for adolescent (12-17 yr): systemic clearance CL = 0.034 ± 0.01 dL/h/kg, terminal half-life $t_{1/2}$ = 14.4 ± 5.5 h. Kogenate FS for adults (≥ 18 yr): systemic clearance CL = 0.033 ± 0.013 dL/h/kg, terminal half-life $t_{1/2}$ = 12.3 ± 3.4 h; and for adolescent (12-17 yr): systemic clearance CL = 0.039 ± 0.015 dL/h/kg, terminal half-life $t_{1/2}$ = 13.1 ± 2.4 h.

Table 1. One-stage clotting assay: PK parameters for BAY 81-8973 and Kogenate FS – subgroups: children / adults (PK analysis population Leopold I Part A)

Parameter [unit]	Children 12 - 17 years (N = 5)		Adults ≥18 years (N = 21)	
	BAY 81-8973	Kogenate FS	BAY 81-8973	Kogenate FS
	Geom. mean (%CV) Arithm. mean ± SD		Geom. mean (%CV) Arithm. mean ± SD	
AUC [IU*h/dL]	979.6 (30.6) 1013.9 ± 286.8	932.8 (33.7) 976.6 ± 352.9	1520.8 (34.2) 1601.3 ± 520.0	1242.3 (38.9) 1325.0 ± 471.5
AUC _{0-tn} [IU*h/dL]	925.4 (29.7) 956.1 ± 265.0	876.8 (35.8) 922.4 ± 347.0	1369.1 (28.2) 1419.0 ± 383.4	1142.4 (36.6) 1209.0 ± 398.6
C _{max} [IU/dL]	88.4 (30.8) 91.7 ± 28.7	107.2 (20.3) 108.9 ± 22.2	98.6 (15.1) 99.7 ± 14.9	99.9 (20.1) 101.9 ± 22.0
C _{max, norm} [kg/dL]	1.77 (30.8) 1.83 ± 0.57	2.14 (20.3) 2.18 ± 0.44	1.97 (15.1) 1.99 ± 0.30	2.00 (20.1) 2.04 ± 0.44
t _½ [h]	11.7 (9.8) 11.7 ± 1.11	10.9 (21.3) 11.1 ± 2.6	13.8 (27.7) 14.3 ± 3.7	12.5 (25.4) 12.9 ± 3.1
MRT _{IV} [h]	16.1 (4.9) 16.1 ± 0.8	14.3 (13.8) 14.4 ± 2.0	19.0 (31.1) 19.8 ± 5.7	16.6 (29.5) 17.3 ± 4.6
V _{ss} [dL/kg]	0.82 (27.7) 0.85 ± 0.24	0.77 (27.4) 0.79 ± 0.20	0.63 (17.0) 0.63 ± 0.11	0.67 (27.8) 0.70 ± 0.21
CL [dL/h/kg]	0.051 (30.6) 0.053 ± 0.017	0.054 (33.7) 0.056 ± 0.016	0.033 (34.2) 0.035 ± 0.012	0.040 (38.9) 0.043 ± 0.017

Table 2. Chromogenic assay: PK parameters for BAY 81-8973 and Kogenate FS – subgroups: children / adults (PK analysis population Leopold I Part A)

Parameter [unit]	Children 12 - 17 years (N = 5)		Adults ≥18 years (N = 21)	
	BAY 81-8973	Kogenate FS	BAY 81-8973	Kogenate FS
	Geom. mean (%CV) Arithm. mean ± SD		Geom. mean (%CV) Arithm. mean ± SD	
AUC [IU*h/dL]	1519.5 (30.1) 1572.0 ± 448.0	1347.6 (38.8) 1424.1 ± 524.7	1989.8 (35.9) 2103.4 ± 702.8	1646.0 (40.0) 1765.2 ± 676.4
AUC _{0-tn} [IU*h/dL]	1292.0 (33.0) 1347.2 ± 440.6	1244.4 (41.1) 1321.2 ± 493.9	1773.2 (33.4) 1860.1 ± 570.2	1508.8 (37.4) 1603.7 ± 568.4
C _{max} [IU/dL]	124.0 (46.4) 132.5 ± 46.3	113.2 (38.1) 118.6 ± 34.7	131.6 (15.8) 133.1 ± 20.4	142.3 (17.7) 144.4 ± 25.7
C _{max, norm} [kg/dL]	2.48 (46.4) 2.65 ± 0.93	2.26 (38.1) 2.37 ± 0.69	2.63 (15.8) 2.66 ± 0.41	2.85 (17.7) 2.89 ± 0.51
t _½ [h]	13.7 (35.9) 14.4 ± 5.5	13.0 (17.3) 13.1 ± 2.4	13.8 (27.0) 14.2 ± 3.5	11.8 (30.3) 12.3 ± 3.4
MRT _{IV} [h]	19.2 (28.4) 19.8 ± 5.8	18.2 (19.9) 18.5 ± 3.9	19.3 (27.2) 19.9 ± 4.9	16.1 (28.8) 16.7 ± 4.4
V _{ss} [dL/kg]	0.63 (57.6) 0.71 ± 0.39	0.67 (51.5) 0.75 ± 0.44	0.49 (21.1) 0.50 ± 0.11	0.49 (23.6) 0.50 ± 0.12
CL [dL/h/kg]	0.033 (30.1) 0.034 ± 0.010	0.037 (38.8) 0.039 ± 0.015	0.025 (35.9) 0.027 ± 0.010	0.030 (40.0) 0.033 ± 0.013

Repeated PK evaluation (Part B):

Nineteen of the subjects who had participated in Part A and continued treatment in Part B had valid PK measurements from both periods. The rFVIII concentration-time curves as displayed in Figure 1 (OC assay) and Figure 2 (CS assay) were similar for BAY 81-8973 in Part A and Part B, *i.e.*, there were no relevant changes in the courses of FVIII concentrations after the first BAY 81-8973 injection and after at least 6 months of prophylaxis treatment.

Based on the CS assay and CS/EP potency assignment for BAY 81-8973 the *in vivo* recovery after the first single dose (IVR \pm SD) was calculated IVR = 2.4 \pm 0.7 IU/dL per IU/kg and for the OC assay IVR = 2.2 \pm 0.4 IU/dL per IU/kg. These IVR values were comparable to those calculated after 6 months of prophylactic treatment.

Summary

- The PK profile of BAY 81-8973 after single-dose administration (50 IU/kg) was at least non-inferior to that of Kogenate FS.
- FVIII plasma concentrations, determined both with the one-stage assay and the chromogenic assay, indicated a more favorable PK profile of BAY 81-8973 than of Kogenate FS in terms of a higher AUC, prolonged t_{1/2} and MRT and a lower CL (all exploratory p-values <0.02, ANOVA), and comparable for C_{max} and V_{ss} values (all exploratory p-values >0.3).
- Repeated PK measurements after 6 to 12 months of prophylaxis treatment with BAY 81-8973 did not indicate any relevant changes in PK characteristics after long-term treatment.

Figure 1. One-stage assay: Concentration time profile of FVIII concentrations (IU/dL) following administration of 50 IU/kg BAY 81-8973 in Part A and B – geometric means (SD) (PK analysis population Part A/B)

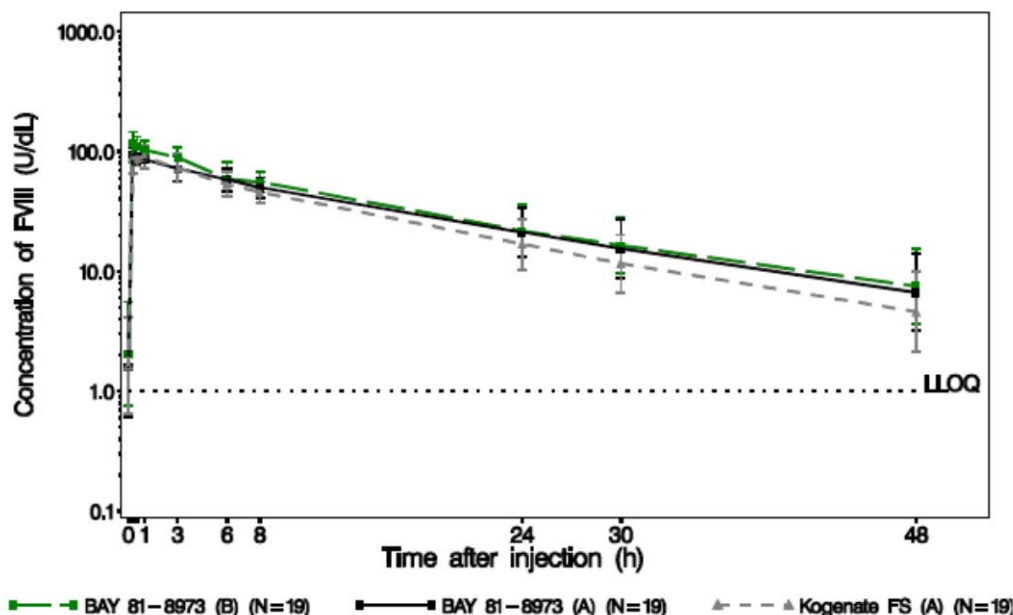
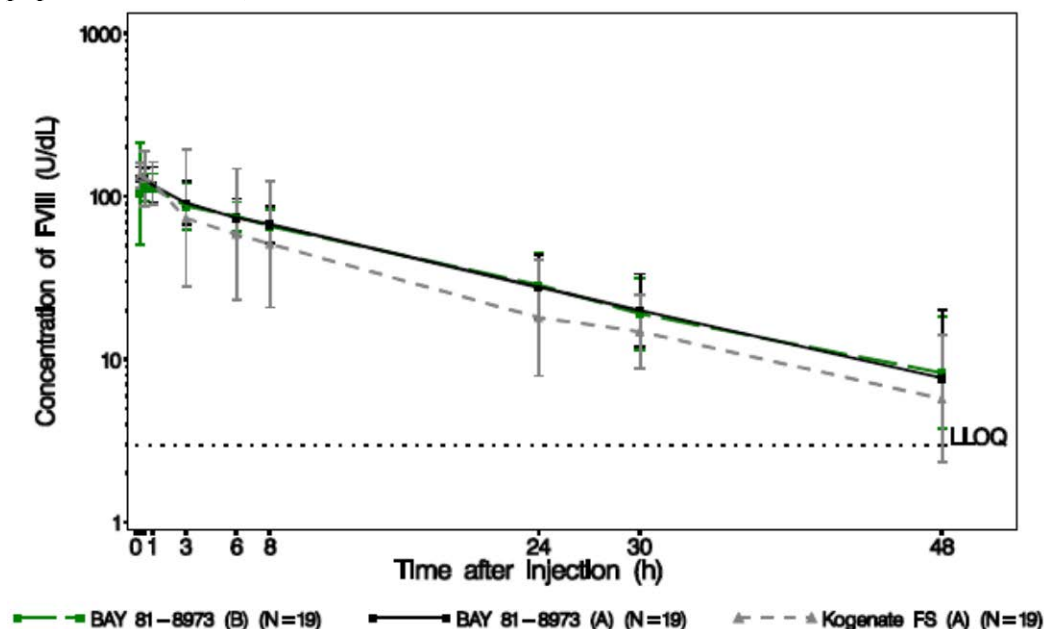


Figure 2. Chromogenic assay: Concentration time profile of FVIII concentrations (IU/dL) following administration of 50 IU/kg BAY 81-8973 in Part A and B – geometric means (SD) (PK analysis population Part A/B)



2. Study Title: A Phase II/III, randomized, cross-over, open-label trial to demonstrate superiority of prophylaxis over on-demand therapy in previously treated subjects with severe hemophilia A treated with plasma protein-free recombinant FVIII formulated with sucrose (BAY 81-8973). Report No. PH-37042 (“Leopold 2”)

Study objectives

Primary objective:

- To demonstrate the superiority of prophylaxis over on-demand therapy by a clinically significant decrease in bleeding rate following 12 months of treatment with BAY 81-8973.

Exploratory objectives (Clinical Pharmacology relevant):

- To compare *in vivo* recovery at the beginning and end of the 6 month periods based on potency determinations (CS/EP versus CS/ADJ) during prophylaxis treatment with BAY 81-8973.

- To evaluate the potential for inhibitory antibody formation to BAY 81-8973 during study treatment.

Study Design:

PK evaluations were only performed in subjects recruited at centers in Japan, and who were willing to participate in this optional investigation.

Four subjects participated in the PK study. According to the protocol, all subjects were to be given a dose of 50 IU/kg based on CS/EP potency assignment. The IV-infusion was administered over 10 min (1 subject over 30 min).

Bioanalytical Methods and Data Analysis:

FVIII activity levels were determined with the one-stage clotting (OC) assay and the chromogenic (CS) assay. The PK parameters were calculated using the model-independent (non-compartment) method

(b) (4) in conjunction with the (b) (4)

Results:

PK evaluations in this study were limited to the data of 4 subjects from Japan. Based on the OC-assay (potency assignment: CS/EP) relevant PK parameters of BAY 81-8973 were estimated as follows (arithmetic mean \pm SD): systemic clearance $CL = 0.033 \pm 0.01$ dL/h/kg and terminal half-life $t_{1/2} = 11.9 \pm 3.3$ h. Incremental in-vivo recovery $IVR = 2.1 \pm 0.5$ IU/dL per IU/kg. Comparable values were calculated for the CS assay. Results based on the CS-assay: $CL = 0.031 \pm 0.008$ dL/h/kg, and $t_{1/2} = 13.0 \pm 3.0$ h. $IVR = 2.1 \pm 0.5$ IU/dL per IU/kg.

Summary:

PK evaluations in Leopold 2 were limited to the data of 4 subjects from Japan. Slightly lower concentrations were measured using the OC assay, but mean $t_{1/2}$ values were comparable to the CS assay.

3. Study Title: A multi-center Phase III uncontrolled open-label trial to evaluate safety and efficacy of BAY 81-8973 in children with severe hemophilia A under prophylaxis therapy. Report No. A51496 (“Leopold Kids”)

The submitted report represents the results of the first 6-month treatment period (Part A).

Study objectives:

The following objectives were defined for the whole study (Part A and Part B):

Primary objective:

- To evaluate the safety and efficacy of the treatment with BAY 81-8973 for prophylaxis and treatment of breakthrough bleeds in children with severe hemophilia A.

Secondary objectives:

- To assess the safety and efficacy of BAY 81-8973 during surgeries.
- To assess incremental recovery of BAY 81-8973.
- To assess pharmacokinetic parameters in a subset of children [previously treated patients (PTPs) and previously untreated patients (PUPs)].

Study Design:

This is an ongoing Phase-III, multicenter, open-label, uncontrolled study to demonstrate the safety and efficacy of the treatment with BAY 81-8973 for prophylaxis, breakthrough bleeds, and surgery in children with severe hemophilia A.

The study is divided into two parts: Part A enrolled a total of 50 PTPs ≤ 12 years of age (25 subjects $>6 - 12$ years and 25 subjects aged 0 – 6 years). Part B, which is still ongoing, was planned to include at least 25 PUPs. All subjects in Part A and Part B received prophylactic treatment with BAY 81-8973. Subjects in Part A were treated with 25-50 IU/kg at least 2x/week, or more frequently. Suitable subjects were given the opportunity to participate in the optional PK evaluation. The optional PK analysis population consisted of 15 patients, 5 patients aged between 2 and 5 years and 10 patients between 6 and 12 years of age. Patients were administered a dose of 50 IU/kg. Blood samples were obtained at pre-injection and at 20-30 min, 4 h, and 24 h after the end of injection of study medication.

Incremental recovery and trough levels of BAY 81-8973 were assessed in all subjects. Samples for FVIII trough levels were collected in the clinic before the next planned prophylaxis injection as scheduled. FVIII trough levels were determined in the blood samples collected before the scheduled BAY 81-8973 injections at baseline, Month 1, Month 2, and Month 6 (or final visit) in Part A. The measurements were performed at least 48 h after previous injection of BAY 81-8973.

Recoveries were performed in conjunction with planned prophylaxis injections, using the subject’s usual dose (except for optional PK). *In vivo* recovery 20-30 min after the end of the injection was determined at baseline, Month 1, 2 and Month 6 (or final visit). *In vivo* recovery was only measured when the subject was not actively bleeding.

Bioanalytical Method and Data Analysis (PK was optional):

Activity levels of BAY 81-8973 were determined in a central laboratory with the chromogenic assay. The PK parameters were calculated in accordance using the model-independent (compartment-free) method and (b) (4) in conjunction with the (b) (4)

Results:

Based on the CS assay the PK parameters of BAY 81-8973 are shown in Table 1. Relevant parameters were estimated as follows (geometric mean, %-CV). PTPs aged 2-6 yr: systemic clearance CL = 0.037 (25.1%) dL/h/kg, terminal half-life $t_{1/2}$ = 11.8 (27%) h. Incremental in-vivo recovery IVR = 2.1 ± 0.5 IU/dL per IU/kg. PTPs aged 6-12 yr: Systemic clearance CL = 0.043 (34.8%) dL/h/kg, terminal half-life $t_{1/2}$ = 11.9 (16.6%) h. Incremental in-vivo recovery IVR = 2.1 ± 0.5 IU/dL per IU/kg.

Table 1: PK parameters for BAY 81-8973 based on chromogenic assay.

Parameter [unit]	PTPs 0 – <6 years N = 5	PTPs 6 – 12 years N = 10	PTPs Total N = 15
	Geom. mean (%CV) [Min - Max]	Geom. mean (%CV) [Min - Max]	Geom. mean (%CV) [Min - Max]
AUC [IU*h/dL] ^a	1334.3 (29.4) [975; 1785]	1155.4 (34.7) [673; 2016]	1203.9 (32.8) [673; 2016]
AUC(0- t_{last}) [IU*h/dL]	963.6 (20.9) [791; 1345]	853.5 (31.3) [515; 1296]	888.8 (28.1) [515; 1345]
AUC(0- t_{last}) _{norm} [kg*h/dL]	19.55 (17.9) [17.24; 26.26]	17.11 (31.4) [10.30; 25.91]	17.88 (27.7) [10.30; 25.91]
AUC _{norm} [kg*h/dL] ^a	27.17 (25.1) [21.46; 34.85]	23.15 (34.8) [13.47; 40.32]	24.24 (32.2) [13.47; 40.32]
C _{max} [IU/dL]	74.2 (40.5) [43.6; 120.1]	79.8 (23.5) [51.0; 111.3]	77.9 (28.7) [43.6; 111.3]
C _{max, norm} [kg/dL]	1.51 (40.0) [0.87; 2.35]	1.60 (23.1) [1.02; 2.23]	1.57 (28.2) [0.87; 2.23]
t_{max} [h] ^b	0.483 [0.417; 4.167]	0.525 [0.350; 3.917]	0.500 [0.350; 4.167]
$t_{1/2}$ [h] ^a	11.8 (27.0) [9.8; 17.3]	11.9 (16.6) [9.8; 16.0]	11.9 (18.9) [9.8; 17.3]
CL [dL/h/kg] ^a	0.037 (25.1) [0.029; 0.047]	0.043 (34.8) [0.025; 0.074]	0.041 (32.2) [0.025; 0.074]
MRT _{IV} [h] ^a	17.3 (24.9) [14.4; 24.7]	17.6 (15.5) [14.7; 23.3]	17.5 (17.6) [14.4; 24.7]
V _{ss} [dL/kg] ^a	0.64 (20.6) [0.48; 0.77]	0.76 (28.6) [0.55; 1.22]	0.72 (27.1) [0.48; 1.22]

a. n = 4 for PTPs 0 - <6 years

b. median [range]

REVIEWER'S COMMENTS

- In general, the PK results of the clinical studies Leopold 1 and Leopold 2 study are acceptable from a Clinical Pharmacology perspective.
- In Leopold 1 the PK parameters showed substantial variability between the OC assay and the CS assay for both drugs, BAY 81-8973 and Kogenate FS (e.g. %diff in AUC > 30 %).
- PK was optional in the Leopold Kids study. Only data based on the CS assay were submitted.
- Noteworthy is the relative high lower-limits of quantifications (LLOQ) for the CS assay LLOQ = 3 IU/dL.

CLINICAL PHARMACOLOGY LABELING COMMENTS

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Kovaltry temporarily replaces the missing clotting factor VIII that is needed for effective hemostasis.

12.2 Pharmacodynamics

The activated partial thromboplastin time (aPTT) is prolonged in patients with hemophilia A. Determination of aPTT is a conventional *in vitro* assay for biological activity of factor VIII. Treatment with Kovaltry normalizes the aPTT similar to that achieved with plasma-derived factor VIII.

12.3 Pharmacokinetics

The pharmacokinetic (PK) properties of Kovaltry were investigated in ~~three studies~~ in previously-treated patients (PTPs), adults and children, in comparison to Kogenate FS. For all PK evaluations, 50 IU/kg of Kovaltry or Kogenate FS was administered. Based on the one-stage clotting (OC) assay and the chromogenic substrate (CS) assay, the 90% CIs for the ratio Kovaltry/ Kogenate FS of C_{max} were within the bioequivalence criteria of 0.80 to 1.25. The bioavailability of Kovaltry was non-inferior to that of Kogenate FS. For AUC-values, the 90% CI was calculated from 1.13 to 1.25 (OC assay) and was calculated from 1.11 to 1.28 (CS assay) for FVIII determinations in plasma. Overall, the data demonstrated non-inferiority of PK for Kovaltry as compared to Kogenate FS.

~~. Serial blood samples were collected over 48 hours in adults and 24 hours in children <12 years of age.~~

Adolescents and Adults

Pharmacokinetics ~~was~~ **were** evaluated in 26 PTPs (ages 12 to 61 years) with severe hemophilia A following administration of 50 IU/kg of Kogenate FS or Kovaltry in a randomized cross-over study with at least a ≥ 3 day washout. Results are presented in Table 4 (OC assay) and Table 5 (CS assay) ~~Both products were released using chromogenic assay for this PK evaluation. (Needs to be clarified internally).~~ Repeated PK measurements in 19 subjects following 6 to 12 months of prophylaxis treatment with Kovaltry did not indicate any relevant changes in PK characteristics after long-term treatment.

FDA comment:

1. Please replace the PK parameters in Table 4 and Table 5 with arithmetic mean \pm standard deviation.
2. Consolidate Table 5 with Table 6

Table 4: Pharmacokinetic Parameters [Arithmetic Mean \pm SD Geometric-Mean (%CV)] for Kovaltry Compared to Kogenate FS, One-Stage Clotting Assay Results

Parameter [unit]	Kovaltry			Kogenate FS		
	12 to 17 yrs (N=5)	≥ 18 yrs (N=21)	Total (N=26)	12 to 17 yrs (N=5)	≥ 18 yrs (N=21)	Total (N=26)
AUC [IU*h/dL]	979.6 (30.6)	1520.8 (34.2)	1397.5 (37.9)	932.8 (33.7)	1242.3 (38.9)	1175.7 (39.2)
C_{max} [IU/dL]	88.4 (30.8)	98.6 (15.1)	96.6 (18.8)	107.2 (20.3)	99.9 (20.1)	101.3 (19.9)
$t_{1/2}$ [h]	11.7 (9.8)	13.8 (27.7)	13.4 (26.0)	10.9 (21.3)	12.5 (25.4)	12.2 (24.9)

MRT _{IV} [h]	16.1 (4.9)	19.0 (31.1)	18.4 (28.6)	14.3 (13.8)	16.6 (29.5)	16.1 (27.6)
V _{ss} [dL/kg]	0.82 (27.7)	0.63 (17.0)	0.66 (21.8)	0.77 (27.4)	0.67 (27.8)	0.69 (27.7)
CL [dL/h/kg]	0.051 (30.6)	0.033 (34.2)	0.036 (37.9)	0.054 (33.7)	0.040 (38.9)	0.043 (39.2)

Table 5: Pharmacokinetic Parameters [Arithmetic Mean \pm SD Geometric Mean (%CV)] for Kovaltry Compared to Kogenate FS, Chromogenic Assay Results

Parameter [unit]	Kovaltry			Kogenate FS		
	12 to 17 yrs (N=6)	≥ 18 yrs (N=20)	Total (N=26)	12 to 17 yrs (N=5)	≥ 18 yrs (N=21)	Total (N=26)
AUC [IU*h/dL]	1519.5 (30.1)	1989.8 (35.9)	1889.2 (36.1)	1347.6 (38.8)	1646.0 (40.0)	1583.9 (39.9)
C _{max} [IU/dL]	124.0 (46.4)	131.6 (15.8)	130.1 (23.0)	113.2 (38.1)	142.3 (17.7)	136.2 (23.8)
t _{1/2} [h]	13.7 (35.9)	13.8 (27.0)	13.8 (28.0)	13.0 (17.3)	11.8 (30.3)	12.0 (28.2)
MRT _{IV} [h]	19.2 (28.4)	19.3 (27.2)	19.3 (26.8)	18.2 (19.9)	16.1 (28.8)	16.5 (27.4)
V _{ss} [dL/kg]	0.63 (57.6)	0.49 (21.1)	0.51 (31.0)	0.67 (51.5)	0.49 (23.46)	0.52 (32.0)
CL [dL/h/kg]	0.033 (30.1)	0.025 (35.9)	0.026 (36.1)	0.037 (38.8)	0.030 (40.0)	0.032 (39.9)

Pediatric PK (Children < 12 Years of Age) and Younger

Pharmacokinetic parameters were calculated from 15 subjects <12 years of age are available for 5 subjects in age group 20 to <6 years of age and 10 subjects in age group 6 to 12 years of age as shown in Table 6. In general, children <12 years of age demonstrated have lower plasma concentrations when as compared to PTP children >12 years of age. The T_{1/2} values across the age groups are is similar. There were no relevant changes for IVR-values over the treatment period of 6 to 12 months.

FDA comment:

1. Please replace the PK parameters in Table 6 with arithmetic mean \pm standard deviation.
2. Table 6 should be consolidated with Table 5

Table 6: Pharmacokinetic Parameters (Arithmetic Mean \pm SD) Geometric Mean [%CV] for Kovaltry in Children <12 Years of age Based on Chromogenic Assay Results

Parameter [unit]	Arithmetic Mean \pm SD Geometric mean (%)		
	PTPs 20 to <6 yrs (N=5)	PTPs 6 to 12 yrs (N=10)	PTPs Total (N=15)
AUC [IU*h/dL]	1334.3 (29.4)	1155.4 (34.7)	1203.9 (32.8)
C _{max} [IU/dL]	74.2 (40.5)	79.8 (23.5)	77.9 (28.7)
t _{1/2} [h] ^a	11.8 (27.0)	11.9 (16.6)	11.9 (18.9)
CL [dL/h/kg] ^a	0.037 (25.1)	0.043 (34.8)	0.041 (32.2)
MRT _{IV} [h] ^a	17.3 (24.9)	17.6 (15.5)	17.5 (17.6)

V _{ss} [dL/kg] ^a	0.64 (20.6)	0.76 (28.6)	0.72 (27.1)
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^an=4 for PTPs 0 to <6 years

FDA comment:

Usually PopPK results are only supportive at best and therefore results will be not included in the package insert.

The PK of Kovaltry is best described by a two-compartment model. The population PK model was developed using the PK and recovery data from 183 subjects who participated in PK evaluations in the three phase III studies. Age, height, weight, body mass index (BMI), lean body weight (LBW) and race were investigated as covariates since they were considered to be of clinical interest. LBW explained a large part of the variability for both clearance and volume of distribution as expected for a compound mainly distributed in plasma.

FDA comment:

Please consolidate (based on assay type) Table 7 and Table 8 with Table 5 and Table 6. Only IVR values obtained at study start should be included

Incremental Recovery

The analysis of all recorded incremental recovery in adult/adolescent PTPs, using one-stage and chromogenic assays, demonstrated a median rise of factor VIII clotting activity (FVIII:C) >2 IU/dL per IU/kg body weight of Kovaltry administered. This result is similar to the reported values for factor VIII derived from human plasma. In children 12 years of age and younger the median incremental recovery values were 1.62 kg/dL for the younger age group (0 to <6 years) and 1.80 kg/dL for the older age group (6 to 12 years). There was no relevant change over the treatment period of 6 to 12 months.

Table 7: Incremental Recovery in Adult PTPs

	Study 1	Study 2	Pooled Analysis
Study participants	N=59	N=56	N=115
Chromogenic assay results Median (Q1; Q3) (IU/dL per IU/kg)	2.5 (2.1; 2.8)	2.1 (1.7; 2.4)	2.3 (1.8; 2.6)
One-stage assay results Median (Q1; Q3) (IU/dL per IU/kg)	2.2 (1.9; 2.5)	2.1 (1.7; 2.3)	2.2 (1.8; 2.4)

Table 8: Incremental Recovery in Pediatric PTPs

Study participants	Study 3	
	PTPs 20 to <6 yrs	PTPs 6 to 12 yrs
	N=24	N=25
Start of study: Chromogenic assay results Median (Q1; Q3) (IU/dL per IU/kg)	1.6 (1.3; 1.9)	1.7 (1.4; 2.0)
	N=23	N=25

After 6 months: Chromogenic assay results Median (Q1; Q3) (IU/dL per IU/kg)	1.8 (1.4; 2.0)	1.8 (1.2; 2.1)
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