Application Type	Original Application
STN	125574/0
CBER Received Date	December 16, 2014
PDUFA Goal Date	March 16, 2016
Division / Office	DHRR /OBRR
Priority Review	No
Reviewer Name(s)	Megha Kaushal
Review Completion Date / Stamped Date	March 10, 2016
Supervisory Concurrence	
Applicant	Bayer HealthCare LLC
Established Name	Antihemophilic Factor (Recombinant), Full Length
(Proposed) Trade Name	KOVALTRY
Pharmacologic Class	Recombinant Full Length
Formulation(s), including Adjuvants, etc	Intravenous Injection
Dosage Form(s) and Route(s) of Administration	Lyophilized Powder in Single Use Vials containing 250, 500, 1000, 2000, and 3000 IU for intravenous use after reconstitution only
Dosing Regimen	Routine Prophylaxis in Adults and Adolescents: 20-40 IU/kg 2 or 3 times per week Routine prophylaxis in Children ≤12 years old: 25-50 IU/kg 2 times per week, 3 times per week, or every other day Control and prevention of bleeding episodes and peri-operative management: Dosing determined by calculations provided in the label using body weight and taking into consideration

	individualized dosing needs.
Indication(s) and Intended Population(s)	On demand treatment and control of bleeding episodes; Perioperative management of bleeding; Routine prophylaxis to reduce the frequency of bleeding episodes in in adults and children with Hemophilia A.
Orphan Designated (Yes/No)	No

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GLOSSARY

ABR	Annualized Bleeding Rate
ADR	Adverse Drug Reaction
AE	Adverse Event
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
BU	Bethesda Unit
CMC	Chemistry, manufacturing, and controls
CI	Confidence Interval
eCTD	Electronic Common Technical Document
ED	Exposure Days
GCP	Good Clinical Practices
IU	International Units
PK	Pharmacokinetic
PMC	Postmarketing commitment
PMR	Postmarketing requirement
PREA	Pediatric Research Equity Act
PTP	Previously Treated Patient
PUP	Previously Untreated Patient
PVP	Pharmacovigilance Plan
rFVIII	Recombinant Human FVIII
SAE	Serious Adverse Event

1. Executive Summary

STN 125574 is an original biologics license application (BLA) submitted by Bayer for the recombinant coagulation factor VIII (rFVIII) product formulated with sucrose and under the proposed trade name KOVALTRY. KOVALTRY is a full length recombinant human factor FVIII produced in baby hamster kidney (BHK) cells and the active ingredient is claimed to be (b) (4) to the currently marketed product Kogenate FS. KOVALTRY has the same rFVIII protein concentration as Kogenate FS, which is licensed in the U.S. under STN 103332. Key changes to the drug substance production method used for Kogenate FS (referred to as Kogenate) in the production of KOVALTRY include:
(b) (4)

Clinical trials that provided the evidence for safety and efficacy of KOVALTRY were conducted under IND 14035. Data from the completed pharmacokinetic (Protocol 12954 Part A and Part B), adolescent and adult Protocol 12954 and 14319), pediatric (Protocol 13400), and extension (Protocol 13400) studies were included for review.. Studies 12954 and 14319 were the primary studies intended to support the marketing approval of KOVALTRY under this BLA submission. These studies were reviewed to evaluate the efficacy and safety of KOVALTRY for the following target indications for use in adults and children with Hemophilia A (HA):

- on-demand treatment and control of bleeding episodes
- perioperative management of bleeding
- routine prophylaxis treatment to reduce the frequency of bleeding episodes

The safety and efficacy of KOVALTRY was evaluated in a total of 193 individual PTPs with severe Hemophilia A (factor VIII less than 1% of normal), who received at least one dose of KOVALTRY in the three multicenter, open label clinical studies submitted in support of this application. All studies have been completed except for Part B of the pediatric study (Protocol 13400-ongoing) investigating previously untreated patients (PUPs).

"Leopold I" (Protocol 12954) was a phase 1, and 2/3 multicenter, open-label, non-inferiority, partially controlled pharmacokinetic (PK), cross over clinical trial in adolescents and adults (age>12years to <65 years). The study was comprised of 4 parts with (A) assessment of PK of KOVALTRY compared to Kogenate, (B) one year prophylaxis treatment with KOVALTRY, (C) hemostatic outcome of treatment of patients undergoing surgery, and (D) an optional one year extension phase. All subjects had severe hemophilia A (FVIII<1%). All were male and all had significant exposure to FVIII products (>150 exposure days (EDs) in adults) at the time of entry into the trial. This study included 28 subjects in Part A, 62 subjects in Part B (10 subjects between 12 and 17 years of age), and 7 subjects in Part C. The results from this study showed, based on PK analyses, that KOVALTRY was non-inferior compared to Kogenate after a single dose administration and indicated a longer half-life for KOVALTRY. Safety and efficacy of treatment with KOVALTRY (routine prophylaxis) was investigated for one year with two methods for potency assignment (chromogenic assay and one-stage adjusted assay). The prophylactic efficacy dose of 20-50 IU/kg 2-3x/week was used, and the mean and median annual bleeding rate (ABR) for the ITT population was 3.8 ± 5.2 and 1 bleed/year, respectively. There were a total of 395 bleeds and 87% were treated with less than 2 infusions and shown to be efficacious in routine prophylaxis. . The hemostatic control during major and minor surgeries was good or excellent in all cases. KOVALTRY exhibited an excellent safety profile. No immunogenicity was detectable.

"Leopold II" (Protocol 14319) was a phase 2/3 study including 80 adolescent and adult PTPs (age>12years to <65 years) with severe Hemophilia A. Ten PTPs were adolescents aged between 14 and 16 years. This study demonstrated superiority of prophylaxis over on demand treatment to reduce the frequency of bleeding episodes with the 2 types of potency assignments. The median ABR was 60 bleeds per year during on demand treatment versus 2 bleeds per year in the prophylaxis group.

KOVALTRY was used in 13 major surgical cases and 46 minor surgical cases in 43 subjects to support the indication for perioperative surgical prophylaxis. Efficacy was rated at good or excellent in 100% of both the major and the minor cases.

"Leopold Kids" (Protocol 13400) was a multicenter, open-label, single arm phase 3 trial which included 51 subjects were children aged 1 to 11 years, with severe hemophilia, >50 EDs and no inhibitor history who received prophylactic treatment with KOVALTRY. PK was evaluated in 12 subjects. Twenty-three subjects remained bleed-free during the 6 month treatment period. The median ABR was 1.90 bleeds per year during prophylaxis. The majority of bleeds were successfully treated with ≤ 2 injections. The treatment with Kovaltry was safe and well tolerated. One subject developed a low titer neutralizing antibody to FVIII.

There were no deaths in the study. There was a total of 27 SAEs reported. Across all trials there were 133/193 (69%) subjects who reported at least one AE. There was only one subject who discontinued treatment due to an AE. The most common adverse drug

reactions in ≥3% in subjects were headache, pyrexia, and pruritus. There was one report of an inhibitor in a PTP. In the ongoing PUPs study, there were 6 cases of FVIII inhibitor formation.

This submission triggers PREA and the PERC meeting was held on October 7 h, 2015. Post marketing commitment studies are required for this product, including the ongoing extension trial and PUPs study.

Conclusion and Recommendation:
Based on the review of the submitted data, KOVALTRY appears safe and efficacious in adults and children with Hemophilia A for the three indications being sought (on demand treatment and control of bleeding episodes; Perioperative management of bleeding; Routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with Hemophilia A.) The BLA is recommended for approval from the clinical perspective.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

All subjects were male. The median age in the adults' studies was 30. The median age in the pediatric study was 6 years of age. The predominant races represented in the study were white and Asian.

Demographics and Baseline Characteristics:

Demographics				
		Leopold I Part B	Leopold II	Leopold Kids
	n		On demand; low dose; hi dose	
Age (years)	Mean ± SD	31.5± 12.7	31.4±10.9; 28.8±10.9; 29.1±11.5	6.4±3
Race (n, %)	White	55 (88.7%)	6 (28.6%); 16 (57.1%); 14 (45.2%)	48 (94.1%)
	Black	4 (6.5%)	3 (14.3%; 0 (0%); 1 (3.2%)	3 (5.9%)
	Asian	0 (0%)	9 (42.9%); 3 (32.1%); 14 (45.2%)	0 (0%)
Ethnicity (n, %)	Hispanic or Latino	2 (3.2%)	3 (14.3%); 3 (10.7%); 2 (6.5%)	1 (2%)

There were no American Indians, Native Alaskans, Hawaiian, or Pacific Islanders included in the study.

The limited sample size in blacks, and hispanics makes it challenging to reach conclusions about the efficacy of KOVALTRY in these races and ethinicities. Since the predeliction for clinical bleeding is dependent on the degree of factor VIII deficiency, race and ethnicity related differences in efficacy are expected to be minimal. Therefore, it is reasonable to extrapolate from Whites/Asians to the other races and ethnic groups.

2. Clinical and Regulatory Background

Currently, there are over ten licensed rFVIII products. Bayer HealthCare has produced 2 recombinant FVIII products, Kogenate (approved in 1993) and was successively

replaced by Kogenate FS, formulated with sucrose and approved in 2000 and marketed in 81 countries. These products are indicated for the control and prevention of bleeding episodes in adults and children (0-16 years) with HA, perioperative management in adults and children with HA, and routine prophylaxis to reduce the frequency of bleeding episodes and the risk of joint damage in children with HA. Subsequently, KOVALTRY has been developed with the introduction of multiple manufacturing processes which has been simplified allowing for faster production time and optimal yields of rFVIII products which reflects a more consistent structure of human FVIII protein.

2.1 Disease or Health-Related Condition(s) Studied

HEMOPHILIA A (CONGENITAL FVIII DEFICIENCY)

Hemophilia A is an X-linked congenital bleeding disorder caused by a deficiency of functional clotting factor VIII which manifests as bleeding episodes (BEs). It is the most common of the severe inherited coagulopathies with an incidence of approximately 1 in 10,000 births, with approximately 20,000 affected males in the United States. The relationship of bleeding severity correlates with clotting factor level. Patients with <0.01 IU/ mL or <1% of functional FVIII are categorized as severe with spontaneous bleeding into joints or muscles. Moderate severity and mild severity have clotting factor levels of 1-5% and 5 to<40%, respectively.

The average life expectancy was less than 20 years with quality of life severely limited by joint complications and intracranial hemorrhage. To prevent joint destruction, the standard of care for children with severe HA is primary prophylaxis with infusions of FVIII. These regular infusions are initiated at the time of the first bleeding episode in a joint or earlier aiming to prevent joint damage. However, inhibitory antibodies to infused FVIII products develop in a substantial percentage of patients treated with either plasma-derived or recombinant FVIII products, making usual treatment with FVIII complicated. Prophylaxis has been shown to prevent complications later in life and to decrease the incidence of inhibitor formation.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

In the late 1950's and much of the 1960's, fresh frozen plasma was the mainstay of treatment for hemophilia A. Cryoprecipitated plasma was introduced in the mid-1960s, and by the late 1960's lyophilized FVIII concentrates from pooled plasma became available. By the 1970's and early 1980's, the use of non–virally inactivated plasma-derived clotting factor concentrates resulted in an epidemic of blood-borne viruses (hepatitis B virus, hepatitis C virus and human immunodeficiency virus). The successful cloning of the factor VIII gene in 1984 allowed for the production of rFVIII. Clinical trials in humans began three years later, and products were widely available after 1994. The advantages of recombinant products includes less viral contamination as compared to plasma-derived products and the potential to produce bioengineered products for improved therapeutics; however, the discordance of labeled units (in vitro) versus recovery in patients (in vivo), differences in laboratory assay methods, and the potential for pathogenic virus from hamster cell cultures were some of the disadvantages.

The first generation licensed rFVIII products was produced in hamster cells and included Recombinate (b) (4); also claimed by Wyeth as Recombinate was developed by Genetic

Institutes, which today is part of Wyeth; approved in 1992) and Helixate FS (Bayer; approved in 1993). These products used media enriched with human or animal plasma proteins for initial cell culture and contained Albumin in the final formulation. For second generation products, such as Helixate FS/Kogenate FS (Bayer/CSLB) and ReFacto (Wyeth), sucrose was substituted for albumin in the final formulation. Third generation products, such as Advate (Baxter) and Xyntha / ReFacto AF (Pfizer) do not contain any human or animal plasma proteins in the purification or final formulation.

Additional therapeutic options include:

- Antifibrinolytic therapies to delay clot dissolution can be used as a secondary, nonspecific, adjunctive therapy but are not primary treatment options. These medications, such as epsilon-aminocaproic acid and tranexamic acid help preserve the hemostatic plug. They are typically used for mucocutaneous bleeding from the mouth or nose and for dental procedures.
- Desmopressin (DDAVP) is an arginine vasopressin analogue that causes a transient rise in FVIII and von Willebrand factor and typically used for mild hemophilia.

2.3 Safety and Efficacy of Pharmacologically Related Products

Inhibitor formation and pathogen transmission are the main safety concerns when treating hemophilia A patients with FVIII replacement therapy. FVIII concentrates derived from human plasma first became available in the 1960s. The high risk of viral transmission from human plasma donors, highlighted by the HIV epidemic in the 1980s, led to the development of rFVIII products which became available in the 1990s. The rFVIII products are genetically engineered and manufactured from animal cell lines, thus minimizing the risk of transmission of human pathogens. Full-length and modified rFVIII have been produced in Chinese hamster ovary (CHO) or baby hamster kidney (BHK) cells. In addition to the risk of pathogen transmission, the development of neutralizing antibodies or inhibitors has been and remains the most concerning safety issue following the administration of FVIII concentrates. The etiology of the development of inhibitors is thought to be a host immune response triggered by non-human proteins contained in the final recombinant FVIII product. Purification steps in the manufacturing processes of successive generations of rFVIII aim to reduce both the transmission of pathogens and the development of inhibitors, which occurs in up to 30% of patients with severe Hemophilia A. [1]

The development of inhibitors decreases the efficacy of replacement therapy, necessitates FVIII dosage increases and/or the use of “bypass” agents, increases the risk of unmanageable bleeding and increases cost of treatment (by 3-5 fold)[2]. The incidence of inhibitor development is approximately 30% in severe disease and less in mild or moderate disease. The highest incidence is in previously untreated patients with severe disease (reported incidence from 3-52%). Inhibitor development in previously treated patients who have not previously developed a FVIII inhibitor is less, reported as 0.9-4%. Potential risk factors for inhibitor development include genetic factors such as the type of FVIII gene mutation, human leucocyte antigen (HLA) type, polymorphisms in immune regulatory regions, family history of inhibitors and ethnic background as well as immunologic environment during early treatment and high intensity of treatment (either peak acute treatment or high overall treatment frequency). The reported incidences of inhibitor formation in trials enrolling PTPs with a history of at least 150 exposure days

(EDs) with comparator products has been reported as 0-2.3% (Kogenate), 0.5-0.9% (Advate), 2.9% (Recombinate), 0.9-2.2% for ReFacto/Xyntha BDD, and 0% (Eloctate). Post marketing, Kogenate FS has been associated with a higher risk of inhibitor development in previously untreated patients with severe HA compared to Advate (Baxter) in recently published studies (RODIN, French National Registry, and United Kingdom Hemophilia Centre Doctors' Organization). Due to these recent findings, this trend constitutes a safety concern in the PUPs populations and revisions to the Kogenate FS PI have been addressed.

KOVALTRY is produced from BHK cells and production with a new cell bank which includes the gene for human heat shock protein (HSP70), removal of all human and animal derived additives from the cell culture and purification processes, introduction of new isolation technology, and introduction of a virus filtration step in efforts to reduce immunogenicity.

1) Gouw SC, van der Bom JG, Ljung R, *et al*. Factor VIII products and inhibitor development in severe hemophilia A. *N Engl J Med*. 2013;368:231-9.
2) Goudemand J.Treatment of patients with inhibitors: cost issues. *Haemophilia* 2013;5:397-491.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

At the time of the BLA submission KOVALTRY was not licensed in any other country.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

FDA had multiple interactions with the applicant throughout the IND and BLA process. A pre-IND meeting occurred in November 2008. An end of phase 2 meeting outlined key CMC, non-clinical, and clinical comments to the applicant. Agreements were made on the strategy for process validation, labeling for joint outcome data generated with Kogenate to be cited if KOVALTRY was comparable to Kogenate without any safety concerns, and to propose a new proprietary name. A written response in October 2013 covered CMC issues. FDA had a pre-BLA meeting with the applicant in April 2014. There were no major agreements reached during this telecon regarding the clinical studies intended for this marketing application. A final telecom regarding the interim study data from the ongoing previously untreated patients' study was agreed to be included in the final PI.

2.6 Other Relevant Background Information

Kogenate FS, the second generation, recombinant full length, formulated with sucrose and approved in 2000 and marketed in 92 countries. These products are indicated for the control and prevention of bleeding episodes in adults and children (0-16 years) with HA, perioperative management in adults and children with HA, and routine prophylaxis to reduce the frequency of bleeding episodes and the risk of joint damage in children with HA. Post marketing, there have been five published studies that have evaluated Kogenate FS and its association with a possible higher risk of inhibitor development in previously untreated patients with severe HA compared to Advate (Baxter). Three studies (RODIN, French, and UK)[1,2,3] show a trend towards an increased risk of inhibitor

development in PUPs as compared to the reference rFVIII product. A survey of Canadian hemophilia centers (2005-2012)[4] and data from the EUHASS registry[5] from 2009-2013, reported an inhibitor development rate in PUPs for Kogenate FS with no statistically significant differences observed across FVIII products. Due to these recent findings, this trend constitutes a safety concern in the PUPs populations and revisions to the PI have been addressed to the sponsor.

1) Gouw SC, van den Berg HM, et al: Intensity of factor VIII treatment and inhibitor development in children with severe hemophilia A: the RODIN study. Blood 121(20): 4046-4055, 2013.
2) Calvez T, Chambost H, et al: Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A. Blood 124(23): 3398-3408, 2014.
3) Collins PW, Palmer BP, et al: Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe hemophilia A, 2000-2011. *Blood* 124(23): 3389-3397, 2014.
4) Vezina C, Carcao M, et al: Incidence and risk factors for inhibitor development in previously untreated severe haemophilia A patients born between 2005 and 2010. *Haemophilia* 20(6): 771-776, 2014.
5) Fisher K, Lassila, R, et al. Inhibitor development in haemophilia according to concentrate: Four-year results from the European Haemophilia Safety Surveillance (EUHASS) project. *Thromb Haemost* 113.4, 2015.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The BLA was submitted electronically and formatted as an electronic Common Technical Document (eCTD) according to FDA guidance for electronic submission. This submission consisted of the five modules in the common technical document structure. It was adequately organized and integrated to conduct a complete clinical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

In order to assess compliance with GCP and to verify the submitted safety and efficacy data against source documents, a Good Clinical Practice (GCP) inspection of selected study sites was done. CBER Bioresearch Monitoring (BIMO) issued inspection assignments at:

- California- 14006 (3 subjects) LEOPOLD I
- Romania- 82001 (4 subjects) LEOPOLD II
- Romania- 82002 (8 subjects) LEOPOLD II

Two of the clinical investigator inspections did not reveal significant problems in the study conduct. The inspection of the third clinical investigator noted significant problems that impact the data, and BIMO recommend that data from this site be excluded from final analyses. In addition, based on our review of the European Medicines Agency (EMA) inspection reports we recommend that the data for all eight subjects at Site #54005 and subject (b) (6) be excluded from final analyses. Please see below for full details.

3.3 Financial Disclosures

Financial certification and disclosure information (Form 3454) have been submitted for both US and non-US sites. No questions about the integrity of the data were raised.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

KOVALTRY is a full length recombinant human factor VIII produced in baby hamster kidney (BHK) cells. The manufacturing process for KOVALTRY was developed based on that of the current commercial Antihemophilic Factor (recombinant) formulated with sucrose (Kogenate-FS) under STN 103332. Key changes to the drug substance production are the following: (b) (4)

4.2 Assay Validation

The manufacturing process for KOVALTRY is considered to be adequately validated at the commercial scale and is sufficiently controlled to assure consistent manufacture of the commercial product that meets acceptable release specifications. The manufacturing process provides acceptable safety margins regarding adventitious agents.

4.3 Nonclinical Pharmacology/Toxicology

Animal studies with KOVALTRY showed the expected pharmacologic (pro-coagulant) activity in a rodent model of Hemophilia A, and the results were similar to those obtained with other approved human FVIII products. There was no evidence of undesirable secondary pharmacologic activity, i.e., thrombogenesis, in FVIII-replete rats and rabbits dosed with KOVALTRY at dose levels up to 8-fold greater than the equivalent human KOVALTRY starting dose. These data were used as proof-of-concept to support the rationale for entering KOVALTRY into clinical trials. Overall, the nonclinical safety profile of KOVALTRY did not identify any unexpected findings or significant concerns in toxicity studies conducted in wild-type, FVIII-replete rabbits and rats. Animal findings for toxicity studies were expected and consistent based on exaggerated pharmacologic effects for recombinant and plasma derived FVIII products.

4.4 Clinical Pharmacology

The clinical pharmacology of KOVALTRY in patients with severe Hemophilia A was evaluated in Leopold I and II. The following conclusions can be drawn from clinical pharmacology studies:

- The PK profile of KOVALTRY after single-dose administration (50 IU/kg) was at least non-inferior to that of Kogenate FS.
- In the repeat PK study, the PK parameters following the first dose were comparable with the PK parameters following 6 months of prophylactic treatment.
- PK study in Japanese subjects was limited to 4 subjects. Slightly lower concentrations were measured using the OC assay, but mean half-life values were comparable to the CS assay.

- Based on the CS assay, the clearance of KOVALTRY was 37% and 59% higher (body weight adjusted) in children 0 – < 6 years and 6 – 12 years of age, respectively.

4.4.1 Mechanism of Action

KOVALTRY temporarily replaces the missing clotting factor VIII needed for effective hemostasis in patients with hemophilia A. Upon activation of the clotting cascade, FVIII is converted to activated FVIII and acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X on phospholipid surfaces, which ultimately converts prothrombin to thrombin and leads to the formation of a fibrin clot.

4.4.2 Human Pharmacodynamics (PD)

Plasma FVIII activity, as measured by a validated one-stage activated partial thromboplastin time (aPTT) clotting assay, is the primary marker for PD/PK determinations of FVIII products in human clinical samples. Plasma clotting time as measured by the aPTT is prolonged in patients with Hemophilia A. Treatment with KOVALTRY normalizes the aPTT.

4.4.3 Human Pharmacokinetics (PK)

The PK of KOVALTRY was characterized based on the plasma FVIII activity profiles as measured by the one-state aPTT and the chromogenic substrate assays.

4.5 Statistical

Briefly discuss the findings of the statistical reviewer. In many cases, this can be achieved in one sentence, such as, "The statistical reviewer verified that the primary study endpoint analyses cited by the applicant were supported by the submitted data."

If the statistical review reveals an issue that could have an effect on the evaluation of the clinical data, summarize at a high level the conclusion(s) of the statistical reviewer with regard to the issue(s).

The statistical reviewer verified that the primary study endpoint analyses cited by the applicant were supported by the submitted data.

4.6 Pharmacovigilance

The applicant commits to the following PMCs:

1. Bayer HealthCare LLC commits to collecting additional safety and efficacy information of KOVALTRY in patients with hemophilia A in a clinical study in 25 previously untreated patients under Protocol 13400 *"A multi-center Phase III uncontrolled open-label trial to evaluate safety and efficacy of BAY 81-8973 (KOVALTRY) in children with severe haemophilia A under prophylaxis therapy"*

    - Final protocol submission: December 20, 2010 (completed)
    - Study/Clinical trial completion: February 28, 2019

- Final Report submission: August 31, 2019

2. Bayer HealthCare LLC commits to collecting additional safety and efficacy information of KOVALTRY in patients with hemophilia A in an extension clinical study under Protocol 13400 *"A multicenter Phase III uncontrolled open-label trial to evaluate safety and efficacy of BAY 81-8973 (KOVALTRY) in children with severe haemophilia A under prophylaxis therapy"*

    - Final protocol submission: December 20, 2010 (completed)
    - Study/Clinical trial completion: December 31, 2020
    - Final Report submission: June 30, 2021

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

Clinical trials that provided the evidence for safety and efficacy of KOVALTRY were conducted under IND 14035. Data from the completed pharmacokinetic (Protocol 12954 Part A and Part B), pivotal (Protocol 12954 and 14319), pediatric (Protocol 13400), and extension (Protocol 13400) trials were included for review to evaluate the efficacy and safety of KOVALTRY.

Review Responsibilities:

Product and Chairperson:	Natalya Ananyeva
Clinical:	Megha Kaushal
Statistician:	Lin Huo
ClinPharm:	Carl-Michael Staschen/Iftekhar Mahmood
Pharm/Tox:	La'Nissa Baker-Brown
APLB:	Loan Nguyen
BIMO:	Bhanu Kannan
DMPQ:	Lori Peters
OBE:	Marthe Bryant
RPM:	Pratibha Rana

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following materials from the submission were reviewed:

Module	Information
5.2	List of Clinical Studies
5.3.3	PK Study Report
5.3.5	Clinical Study Reports
5.3.5.2	Case Report Forms and Case Report Tabulations
5.4	Literature References

5.3 Table of Studies/Clinical Trials

Study name, Phase	Design Location (no. of centers)	Study objectives	Dose and regimen Treatment duration	Study population	Number of patients by treatment group (Intent-to-treat set) [a]
'*Leopold I*' Report nos. A62366 and PH-37225 (protocol no. 12954)					
Part A Phase 1	Randomized, non-inferiority, single-dose, open-label, intra-individual, cross-over, controlled, pharmacokinetic	To demonstrate the pharmacokinetic (PK) non-inferiority of BAY 81-8973 as compared to Kogenate FS using bioequivalence criteria	50 IU/kg of BAY 81-8973 or Kogenate FS; CS/EP potency (dose) assignment Two single IV injections, and at least a 3-day washout period between treatments	Previously treated patients (PTPs), male, 12-65 years of age	PK analysis[a] (Part A): 26 PK analysis[a] (Parts A+B): 19
Part B Phase 2/3	Randomized, open-label, intra-individual, cross-over for 2 different potency assignments	To demonstrate the efficacy and safety of BAY 81-8973 for the treatment of bleeds and prophylaxis Repeat PK	20-50 IU/kg of BAY 81-8973, CS/EP and CS/ADJ potency assignment[b] 2 to 3 times per week 12 months in total, with 6 months per potency (CS/EP and CS/ADJ) assignment	PTPs, male, 12-65 years of age	CS/EP → CS/ADJ: 30 CS/ADJ → CS/EP: 32 Total: 62
Part C Phase 2/3	Open-label	To assess the hemostatic outcome of treatment with BAY 81-8973 during major surgery	Treatment only during hospital stay from pre-operation to their discharge (not exceeding a total of 3 weeks); according to standard practice for the use of Kogenate FS in major surgery (CS/EP potency dose assignment). According to individual need within the scope of surgery	PTPs, male, 12-65 years of age requiring major surgery	Part C only: 5 Including surgery patients from the extension: 10
Extension Phase 3	Open-label	To collect additional safety and efficacy data from the extended treatment period	BAY 81-8973 potency by CS/EP only. Treatment as in Part B, with one-time dose adjustment permitted at start of extension. One more year	Patients who completed Part B and wished to continue	Entered the extension: 55
26 centers in 12 countries: Denmark (1), Germany (1), Hong Kong (1 *[Part A only]*), Israel (1), Italy (4), Spain (4), Poland (2), Sweden (1) *[with 1 screening failure only]*, South Africa (2), Turkey (3), UK (1), US (5)					
'*Leopold II*' Report no. PH-37042 (protocol no. 14319)					
Phase 2/3	Randomized, multicenter, open-label, intra-individual, cross-over for 2 different potency assignments with 2 different prophylaxis dose regimens and an on-demand group	To demonstrate superiority of prophylaxis over on-demand treatment	Prophylaxis group: low dose [20 — 30 IU/kg 2x/week] or high dose [30 — 40 IU/kg 3x/week]; each per potency (CS/EP and CS/ADJ) assignment On-demand group: per potency (CS/EP and CS/ADJ) assignment 12 months in total, with 6 months per potency assignment Dosing for treatment of bleeds according to treatment recommendation for Kogenate FS	PTPs, male, 12-65 years of age	Prophylaxis group: low-dose: 28 high-dose: 31 On-demand group: 21 Total: 80
30 centers in 11 countries: China (5), Czech Republic (1), Japan (4), Mexico (2), Romania (4), Republic of Serbia (4), Russia (2), South Africa (2), Taiwan (1), Turkey (3), US (2)					
'*Leopold Kids*' Report no. A51496 (protocol no. 13400)					
Part A Phase 3	Multicenter, uncontrolled, open-label	To demonstrate the safety and efficacy of treatment with BAY 81-8973 for prophylaxis and breakthrough bleeds in children with severe hemophilia A, optional PK in any part of the study	25 — 50 IU/kg prophylaxis at least 2x/week, treatment of breakthrough bleeds and prevention of bleeds with surgical procedures Approximately 6 months and at least 50 EDs Optional PK measurements (patients to receive exact dose of 50 IU/kg)	PTPs, male, ≤12 years of age	0 to <6 years of age: 25 6 to 12 years of age: 26 Available PK to date: 0 to <6 years of age: 5 6 to 12 years of age: 10
Part B Phase 3	Multicenter, uncontrolled, open-label		15 — 50 IU/kg (minimum dose 250 IU) prophylaxis at least 1x/week, treatment of bleeding events At least 50 EDs	PUPs, male, <6 years of age	Ongoing; preliminary efficacy and safety data provided
Extension Phase 3	Open-label	To collect additional safety and efficacy data from the extended treatment period	As for Parts A and B At least 100 cumulative EDs or until market authorization	Patients who completed Parts A and B and wished to continue	Ongoing; preliminary efficacy and safety data provided
25 centers in 12 countries: Bulgaria (2), Canada (2), Denmark (1), Hungary (3), Ireland (1), Israel (1), Italy (3), Lithuania (1), Latvia (1), Poland (3), Romania (3), US (4)					

Abbreviations: CS/EP = chromogenic substrate assay according to European Pharmacopoeia; CS/ADJ = one-stage assay; ED = exposure days; IU/kg = international unit per kg; PTP = previously treated patient; PUP = previously untreated patient; UK = United Kingdom; US = United States

[a] Except for the population in Part A of Leopold I for pharmacokinetic (PK) analysis, all other populations displayed are the intent-to-treat (ITT) set.

[b] Once assigned a dose, the patient was maintained on that dose for the duration of the study.

Source: BLA 125574/0 5.3.5.3 Summary of Clinical Efficacy:Clinical Development Program Table 1-1 page 11

The clinical development plan was designed to evaluate the bleeding rates based on dosing with 2 potency assignments- chromogenic assay and one-stage assay. The amount of active FVIII in certain batches of KOVALTRY was measured using a chromogenic substrate assay per the European Pharmacopoeia (CS/EP) and using the one-stage coagulation assay for comparison (CS/ADJ), the results revealed a ~20% difference in the amount of active FVIII detected. The amount in the CS/ADJ was

measured ~20% *lower* than the CS/EP. Thus, an average of 20% dose difference was expected between the two groups and the subjects in the CS/EP group received a lower dose. This had potential clinical concerns for underdosing and increased bleeding risk.

Leopold I evaluated the bleeding rates in routine prophylaxis, while Leopold II evaluated the bleeding rates in routine prophylaxis and compared it to rates of those receiving on-demand treatment. Perioperative hemostatic efficacy was evaluated in Leopold I.

5.4 Consultations

In this section, summarize from a clinical perspective any contribution to the evaluation of the application that came from outside the review team and the Division. In general, this section is reserved for documenting recommendations solicited during the review cycle. For example, the merits of a particular clinical endpoint for studying a specific product might be the primary subject of both a workshop convened during Phase 2 and an Advisory Committee held during the review of an application. Discussion of the former belongs in Section 2; the latter, here (under subsection 5.4.1).

Recommendations on specific review issues are received from other FDA groups outside the Division as a matter of routine (e.g., PeRC, CBER's safety working group, etc). This type of input should be discussed in the separate, relevant section. If an appropriate approach is not readily apparent, seek supervisory input.

No consultants were used during the review of this BLA.

5.4.1 Advisory Committee Meeting (if applicable)

There was no advisory committee meeting for the review of this BLA.

5.4.2 External Consults/Collaborations

There were no external consults or collaborations done in the review of this BLA.

5.5 Literature Reviewed (if applicable)

1) Gouw SC, van den Berg HM, et al: Intensity of factor VIII treatment and inhibitor development in children with severe hemophilia A: the RODIN study. Blood 121(20): 4046-4055, 2013.
2) Calvez T, Chambost H, et al: Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A. Blood 124(23): 3398-3408, 2014.
3) Collins PW, Palmer BP, et al: Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe hemophilia A, 2000-2011. *Blood* 124(23): 3389-3397, 2014.
4) Vezina C, Carcao M, et al: Incidence and risk factors for inhibitor development in previously untreated severe haemophilia A patients born between 2005 and 2010. *Haemophilia* 20(6): 771-776, 2014.
5) Fisher K, Lassila, R, et al. Inhibitor development in haemophilia according to concentrate: Four-year results from the European Haemophilia Safety Surveillance (EUHASS) project. *Thromb Haemost* 113.4, 2015.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Protocol 12954- Leopold I
This was 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 in previously treated subjects with severe hemophilia A under prophylaxis therapy.

6.1.1 Objectives (Primary, Secondary, etc)

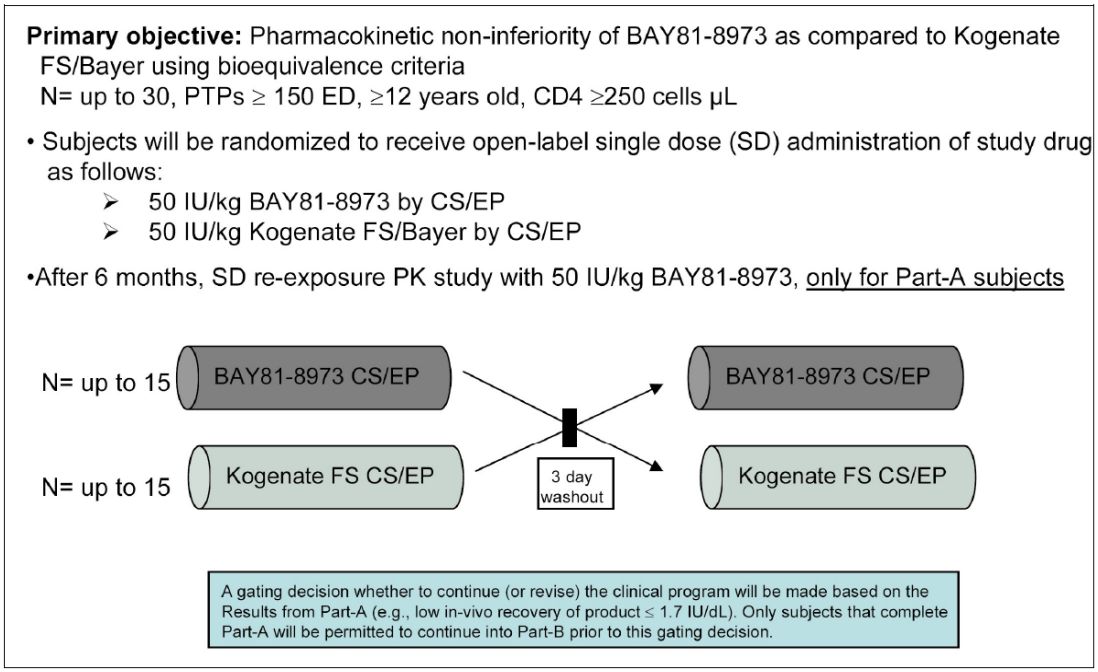
Part A:
- to demonstrate the pharmacokinetic non-inferiority of KOVALTRY as compared to Kogenate FS using bioequivalence criteria following single dose administration.
- to evaluate the *in vivo* recovery of Human factor VIII (FVIII) plasma levels 15 minutes post single injection of KOVALTRY.

Part B:
- was to demonstrate the efficacy and safety of KOVALTRY for the treatment of bleeds and prophylaxis.
The secondary objectives were the following:
- To compare bleeding frequency of prophylactic treatment with KOVALTRY (dose determined by Chromogenic substrate assay per European Pharmacopoeia [CS/EP] versus dose determined by Chromogenic substrate assay/adjusted to one stage assay [CS/ADJ]) as measured by the bleeding rate.
- To compare *in vivo* recovery at the 6 month periods based on potency determinations (CS/EP versus CS/ADJ) during prophylactic treatment with KOVALTRY.
- To evaluate the potential for inhibitory antibody formation during prophylactic treatment with KOVALTRY.
- To evaluate the potential for antibody formation to heat shock protein 70 (HSP-70) and/or hamster proteins during prophylactic treatment with KOVALTRY.
- To evaluate surgical outcomes in terms of hemostasis during treatment with KOVALTRY, including major surgeries of Part B and Part C.
-To assess quality of life (QoL) and pharmaco-economic parameters during prophylactic treatment with KOVALTRY
- To assess the safety and tolerability profile of KOVALTRY by assessing clinical chemistry, hematological parameter, and adverse event (AE) presentation.

6.1.2 Design Overview

Part A: To assess the PK non-inferiority of KOVALTRY to Kogenate FS in up to 30 subjects with severe Hemophilia A using bioequivalence criteria. The dose for both products was determined by the chromogenic Substrate Assay per European Pharmacopeia (CS/EP). This was a single dose, intra-individual, cross-over trial design.

Schematic Trial Design for Part A:



Abbreviations: CS/EP = chromogenic substrate assay per European Pharmacopoeia, ED = exposure day(s), N = number of subjects, PTP = previously treated patients, SD = single-dose.

Source: Original from BLA 125574/0 CSR 12954 Figure 7-1

Part B: To assess the safety, tolerability, and efficacy of prophylaxis treatment using 20-50IU/kg of KOVALTRY administered 2-3x/week to 60 subjects (inclusive of Part A subjects). The dose was determined by CE/EP and CS/ADJ. The subjects were treated with both potency assignments in a cross over design.

Subjects were to undergo prophylaxis for a period of 6 months. The dosage for prophylaxis was 20-50 IU/kg administered 2-3x/week. This dose assignment was maintained for the trial and breakthrough bleed dosing was treated with KOVALTRY. Thereafter, and after a 2-3 day washout period, subjects were to cross over within their treatment group for a 6 month treatment period.
In vivo recovery was to be assessed twice during each period: at the start and at 3 months or at the end of the 6 month potency assignment period.

Reviewer Comment
The dosage for prophylaxis was dosed at 20, 25, 30, 35, 40, or 50 IU/kg and administered 2-3 times per week at the investigator's discretion. Once assigned, this was to be maintained for the duration of the trial. Subjects were allowed to be given extra doses for breakthrough bleeds. There were no clear parameters used for the initial prophylaxis dose, but was likely based on previous bleeding history.

The extension phase was an optional continuation of prophylaxis treatment up to 12 additional months, during which time subjects were treated with KOVALTRY.

Subjects who required major or minor surgery were treated with KOVALTRY and included in the efficacy and safety evaluations.

Part C: A major surgery arm for assessment of outcome with KOVALTRY treatment in additional subjects who did not participate in Part B was included. These subjects received treatment with CS/EP potency assignment.
These subjects were only to receive the study drug during their hospital stay from pre-operation to their discharge.

Reviewer Comment
The overall design of the trial is sufficient to support the proposed indications.

6.1.3 Population

The following criteria were used to evaluate subjects for **inclusion** in the study:

1. Male, aged 12 to 65 years
2. Severe hemophilia A, defined as < 1% FVIII activity (FVIII:C) as determined by one stage clotting assay at the time of screening. If the screening result turns out to be equal to or higher than 1%, then severe hemophilia A may be confirmed by one of the following:
-Documented historical evidence from a recognized (certified) clinical laboratory (acceptable to Global Clinical Lead [GCL]) demonstrating < 1% FVIII:C as determined by one-stage clotting assay
-Assay results from a previous Bayer hemophilia clinical trial
3. At least 150 exposure days (ED) in total with any recombinant FVIII or plasma-derived FVIII. Cryoprecipitate and fresh frozen plasma treatments are not considered in this total.
4. Currently receiving on-demand or any type of prophylaxis treatment regimen with any FVIII product.
5. No current evidence of inhibitor antibody as measured by the Nijmegen-modified Bethesda assay [<0.3 Bethesda units (BU/mL)] in 2 consecutive samples and absence of clinical signs or symptoms of decreased response to FVIII administration. (First negative sample can be historical if obtained within 3 months prior to screening. Second negative, confirmatory sample testing must, in all cases, be performed by a central laboratory using the Nijmegen test. If a first recent sample is not available, then testing for 2 negative samples must be performed by the central laboratory at least 1 week apart). Subjects may not receive FVIII within 72 h prior to the collection of samples for inhibitor testing.
6. No history of FVIII inhibitor formation, defined as inhibitor antibody > 0.6 BU/mL, by the Bethesda assay. However, patients with a maximum historical titer of 1.0 BU with the Classical Bethesda assay on no more than 1 occasion but with at least 3 subsequent successive negative results (<0.6 BU) thereafter are also eligible.
7. Willingness and ability to complete training in the use of the study electronic patient diary (EPD) by the subject or a surrogate (a caregiver or family member over 18 years of age). Note: this criterion does not apply to “Major Surgery Arm population”.
8. Written informed consent by subject and parent/legal representative, if under age of consent per local regulation.

Part C: Additional criteria applicable only to the Major Surgery Arm population
9. Medically requires any type of major surgery which requires treatment with FVIII during the perioperative period.

10. The surgery is scheduled to occur within 6 weeks of screening.

The following criteria were used for the **exclusion** of subjects from the study:

1. Presence of another bleeding disease that is different from hemophilia A (*eg*, von Willebrand disease, hemophilia B).
2. Thrombocytopenia (platelet count < 100,000/mm3).
3. Abnormal renal function (serum creatinine > 2.0 mg/dL).
4. Presence of active liver disease verified by medical history or persistent and increased alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5x the upper limit of normal (ULN) or severe liver disease as evidenced by an international normalized ratio (INR) >4, hypoalbuminemia, and significant portal vein hypertension in the judgment of the investigator.
5. Received treatment with immunomodulatory agents within the last 3 months prior to study entry or requires treatment during the study. [The following drugs are allowed: interferon-α treatment for hepatitis C virus (HCV), highly active antiretroviral therapy (HAART) for human immunodeficiency virus (HIV), and or a total of 2 courses of pulse treatment with steroids for a maximum of 7 days at 1 mg/kg or less].
6. Absolute cluster of differentiation 4 (CD4) lymphocyte cell count < 250 cells/µL.
7. Receiving or has received other experimental drugs within 3 months prior to study entry, with the exception of Bayer Kogenate (Bayer factor VIII study drugs) received in studies within 2 weeks prior to study entry.
8. Requires any pre-medication to tolerate FVIII injections (*eg*, antihistamines).
9. Unwilling to comply with study visits or other protocol requirements or is not suitable for participation in this study for any reason, according to the investigator.
10. Known hypersensitivity to hamster and mouse protein.
11. Any subject who cannot forego at least 3 days without receiving FVIII for washout purposes.

Reviewer Comment
The inclusion and exclusion criteria are acceptable.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Part A – pharmacokinetic study
Test drug: KOVALTRY
Comparator: Kogenate FS (= Kogenate Bayer)
Dosage: Exactly 50 IU/kg (without rounding to full vials), single injection (potency determined by CS/EP)
Route of administration: Manual intravenous (IV) injection over a 10-minute period.
Duration: 2 single injections (1 each of Kogenate FS and BAY 81-8973 according to the randomized cross-over design)

Part B – prophylaxis study
Test drug: KOVALTRY
Dosage: 20-50 IU/kg (20, 25, 30, 35, 40, or 50 IU/kg) *rounded to full vials*, 2-3 times per week (treatment potency assignments determined by CS/EP and CS/ADJ)
Route of administration: Manual IV injection over 1 – 15 minutes.
Duration: 12 months (6 months per mode of potency assignment according to the randomized cross-over design)

Part C – perioperative study
Test drug: KOVALTRY or Kogenate FS; Kovaltry used only after 20 bleeding events had been assessed.
Dosage: potency assignments determined by CS/EP
Route of administration: Manual IV injection over 1 – 15 minutes.
Duration: 12 months (6 months per mode of potency assignment according to the randomized cross-over design)

6.1.5 Directions for Use

No directions for use were provided in the study protocol for review.

6.1.6 Sites and Centers

Subjects were enrolled at 26 study centers in 12 countries (number of recruiting sites in parentheses): Denmark (1), Germany (1), Hong Kong (1 [Part A only]), Israel (1), Italy (4), Spain (4), Poland (2), Sweden (1), South Africa (2), Turkey (3), United Kingdom (1) and United States of America (5).

6.1.7 Surveillance/Monitoring

Part A: The screening period started at Visit 1 (Screening/Baseline) and was completed when all laboratory results necessary to check the subject's eligibility had been received and assessed prior to or at Visit 2. On the first day of the screening period, subjects were to be informed about the study and were to sign the informed consent if they were willing to participate. Subjects who agreed to participate in the study were to be checked against the inclusion and exclusion criteria, and appropriate samples were to be collected for analyses. Subjects were randomized to receive either BAY 81-8973 or Kogenate FS in a single injection over a 10-minute period and blood samples were to be collected over 48 h (Visit 2). After a washout period of at least 3 days, and if the subject had no signs or symptoms of an acute bleeding episode, the subjects were to cross-over to the other treatment and the second, 48-h, single injection PK sampling was to begin (Visit 3). Visit 4, a follow-up visit, 3-14 days after the second PK dose, consisted of safety assessments.

Part B: Self-administration of study drug extended from Visit 2 to Visit 7 for 52 weeks. The treatment period applied to all subjects in the study, independent of individual treatment regimen.
During the subjects' home treatments, the study staff was to make a follow-up phone call to the subjects every 2 weeks to evaluate subjects' proper adherence to home treatments including treatments for bleeds by reviewing the data recorded in their EPD.

Part C: Once the subject's participation had been confirmed, the subjects could be admitted to the hospital for the surgical procedure at Visit 2 which was to take place within 6 weeks of the screening visit. There was to be a safety follow-up 1 week after the final visit. The follow-up was to be conducted by telephone.

6.1.8 Endpoints and Criteria for Study Success

The primary efficacy variable was the ABR for all bleeds (i.e., spontaneous and trauma bleeds, untreated bleeds and bleeds of missing reason) in each 6-month potency assignment period.

Other efficacy variables included:

- Annualized numbers of joint bleeds, spontaneous bleeds, trauma bleeds and bleeds which occurred within 48 h after a prophylaxis injection in each 6-month potency assignment period
- Description of bleeds according to location
- FVIII usage calculation in each 6-month period (CS/EP and CS/ADJ) expressed as number of injections to treat breakthrough bleeds in IU/kg per month per year, as well as IU/kg per event (prophylaxis, breakthrough bleed, and surgery)
- Control of bleeding as measured by the number of injections required to treat a bleed
- Subject's assessment of response in treatment of bleeds, with the hemostatic outcome of bleeding episodes expressed as "poor", "moderate", "good", and "excellent"
- FVIII recovery values in each 6-month potency assignment period
- Hemostatic outcome of surgeries (both major and minor) including blood loss, transfusion, and/or hemostasis-related surgical complications
- Change in QoL (as assessed by Hemophilia-Specific Quality of Life -A questionnaire and European Quality of Life-5 Dimensions Health Questionnaire).

Part C
Hemostatic outcome of surgeries was assessed by the surgeon (including blood loss, transfusion, and/or hemostasis-related surgical complications).

Extension

Primary efficacy variable was the ABR for all bleeds, including spontaneous and trauma bleeds, untreated bleeds, as well as injections with reason for injection "other", which could be a bleed (worst case approach).

Other efficacy variables include:

- Annualized number of total bleeds, joint bleeds, spontaneous bleeds, trauma bleeds and bleeds which occurred within 48 h after a prophylaxis injection
- Description of all bleeds according to location
- Control of bleeding as measured by the number of injections required to treat a bleed
- Subject's assessment of response in treatment of bleeds
- Hemostatic outcome of surgeries (both major and minor)
- Change in QoL.

Criteria for Study Success
If the estimated ratio of annualized bleeding episodes is less than 0.5 (i.e., greater than a 50% reduction) clinical importance of the individualized prophylaxis regimen will have been demonstrated. The safety endpoint with regard to inhibitors would be met if the upper one-sided 97.5% confidence limit was below 6.8%.

6.1.9 Statistical Considerations & Statistical Analysis Plan

In general, continuous variables were summarized by descriptive statistics. Categorical variables were presented with the number and percentage in each category. Statistical tests were performed at the 2-sided, 0.05 significance level, unless otherwise specified. No imputation of data was performed.

Analysis populations

Safety population: All subjects randomized into the study who received study drug or who were surgery-only subjects.

ITT population: All subjects in the safety population who have injection/bleeding data from the EPD and/or case report form (CRF).

PP population: All subjects in the ITT population who have no major protocol deviations and have EPD data from both crossover periods of Part B.

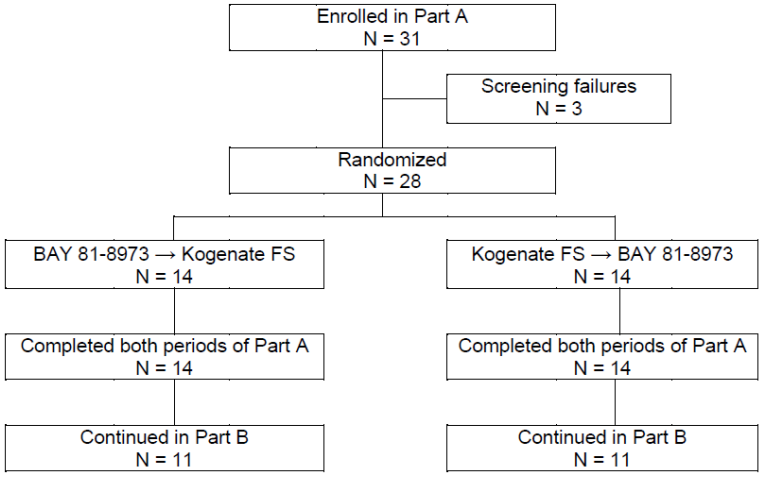
The ITT population was used for the primary analysis. The efficacy analysis of the PP population was supportive.

All available safety and efficacy data from the extension phase were to be analyzed and reported separately after completion of the extension period.

All efficacy variables related to bleeds were to be analyzed by period (CS/EP and CS/ADJ) and for both periods combined using summary statistics.

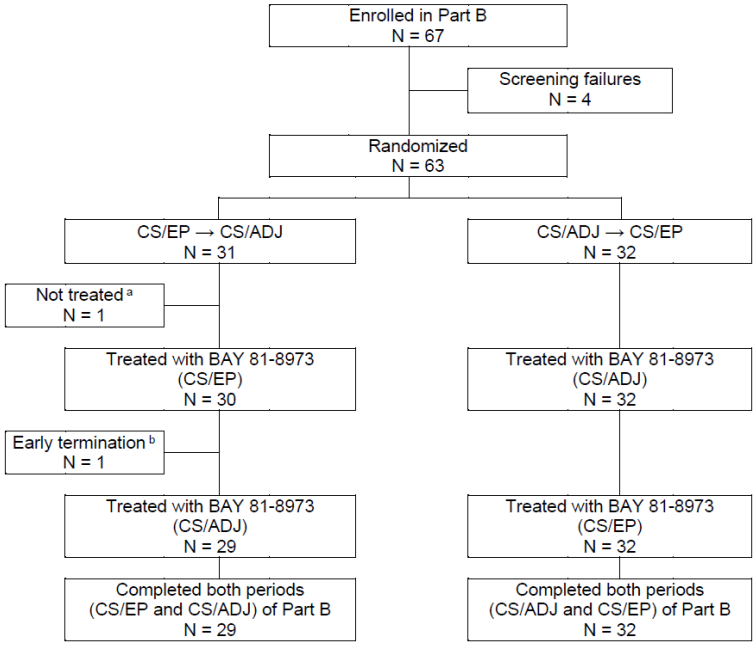
6.1.10 Study Population and Disposition

Part A:
Thirty-one subjects were screened and enrolled. Twenty-eight subjects were randomized to the two treatment sequence groups. All subjects completed the PK evaluations with both drugs. Twenty-two continued into Part B of the study. Nineteen of these subjects completed Part B.



Source: BLA 125574/0 CSR 12954 Figure 8-1

Part B:
The total number enrolled in Part B was 67 with 4 screening failures, thus 63 were randomized. Three subjects of Part B underwent major surgeries during the extension period.



[a] Reason for not being treated: Subject withdrew consent.
[b] Reason for early termination: Protocol violation.
Source: BLA 125574/0 CSR 12954 Figure 8-2

Part C:

Six subjects were enrolled with one screening failure. One subject was enrolled twice for 2 different major surgeries.

6.1.10.1 Populations Enrolled/Analyzed

All of the treated subjects (28 in Part A, 62 in Part B, and 5 in Part C) were included in the safety analysis. PK analyses were performed in 26 subjects in Part A. Nineteen completed part B and had valid PK measurements for both parts and underwent a further PK session at the end of their respective 6 month treatment period.
In Part B, all of the 62 treated subjects were included in the intent to treat population. This combined per protocol population was 59. The safety in major surgeries including those 5 subjects enrolled in Part C and 3 additional subjects during the extension period of Part B.

6.1.10.1.1 Demographics
Twenty-eight males between 12 and 61 years participated in Part A. Five subjects were children ages 12-17 years.

	BAY 81-8973 → Kogenate FS (N = 13)	Kogenate FS → BAY 81-8973 (N = 13)	Total (N = 26)
Sex [n (%)]			
Male	13 (100.0)	13 (100.0)	26 (100.0)
Race			
White	10 (76.9)	8 (61.5)	18 (69.2)
Black	0 (0.0)	1 (7.7)	1 (3.8)
Asian	3 (23.1)	3 (23.1)	6 (23.1)
Hispanic	0 (0.0)	1 (7.7)	1 (3.8)
Age (years)			
n	13	13	26
Mean ± SD	33.2 ± 14.1	28.0 ± 11.9	30.6 ± 13.1
Median	34.0	28.0	29.5
[Min; Max]	[17; 61]	[12; 51]	[12; 61]
Age group [n (%)]			
12 - <18 years	1 (7.7)	4 (30.8)	5 (19.2)
18 - <30 years	4 (30.8)	4 (30.8)	8 (30.8)
30 - <60 years	6 (46.2)	5 (38.5)	11 (42.3)
60 - <65 years	2 (15.4)	0 (0.0)	2 (7.7)
Baseline weight (kg)			
n	13	13	26
Mean ± SD	71.95 ± 14.71	71.88 ± 20.09	71.92 ± 17.25
Median	79.00	68.00	70.60
[Min; Max]	[47.7; 91.0]	[46.0; 119.7]	[46.0; 119.7]
Baseline height (cm)			
n	13	13	26
Mean ± SD	171.7 ± 7.7	170.9 ± 7.8	171.3 ± 7.6
Median	170.0	172.0	171.0
[Min; Max]	[156; 186]	[155; 182]	[155; 186]
Baseline BMI (kg/m^2)			
n	13	13	26
Mean ± SD	24.36 ± 4.50	24.46 ± 5.82	24.41 ± 5.10
Median	25.65	22.99	25.25
[Min; Max]	[18.0; 30.5]	[16.7; 36.9]	[16.7; 36.9]

[a] Underlined numbers changed in CSR Amendment 2 (7.1 changed to 7.7, 3.6 changed to 3.8).

Source: BLA 125574/0 CSR 12954 Table 8-2

Reviewer Comment

The demographics were comparable among the 26 PK subjects analyzed.

Sixty-two males between 12 and 61 years received treatment with KOVALTRY in Part B. A total of 10 subjects were between 12-17 years.

	CS/EP → CS/ADJ (N = 30)	CS/ADJ → CS/EP (N = 32)	Total (N = 62)
Sex [n (%)]			
Male	30 (100.0)	32 (100.0)	62 (100.0)
Race			
White	28 (93.3)	27 (84.4)	55 (88.7)
Black	1 (3.3)	3 (9.4)	4 (6.5)
Hispanic	1 (3.3)	1 (3.1)	2 (3.2)
uncodable	0 (0.0)	1 (3.1)	1 (1.6)
Age (years)			
n	30	32	62
Mean ± SD	30.8 ± 12.8	32.2 ± 12.8	31.5 ± 12.7
Median	29.0	32.0	30.0
[Min; Max]	[13; 59]	[12; 61]	[12; 61]
Age group [n (%)]			
12 - <18 years	5 (16.7)	5 (15.6)	10 (16.1)
18 - <30 years	11 (36.7)	9 (28.1)	20 (32.3)
30 - <60 years	14 (46.7)	16 (50.0)	30 (48.4)
60 - <65 years	0 (0.0)	2 (6.3)	2 (3.2)
Baseline weight (kg)			
n	30	32	62
Mean ± SD	79.90 ± 18.77	74.18 ± 15.23	76.95 ± 17.14
Median	81.60	75.65	77.40
[Min; Max]	[46.0; 121.1]	[39.0; 107.0]	[39.0; 121.1]
Baseline height (cm)			
n	29	32	61
Mean ± SD	175.1 ± 8.5	173.9 ± 8.7	174.5 ± 8.5
Median	176.0	174.0	175.0
[Min; Max]	[148; 192]	[155; 189]	[148; 192]
Baseline BMI (kg/m^2)			
n	29	32	61
Mean ± SD	26.24 ± 4.72	24.46 ± 4.49	25.31 ± 4.65
Median	26.20	24.83	25.59
[Min; Max]	[16.7; 37.4]	[16.2; 32.8]	[16.2; 37.4]

Source: BLA 125574/0 CSR 12954 Figure 8-3

All of the 8 subjects in the major surgery arm were white males with ages ranging from 28-41 years.

Reviewer Comment
Obese subjects with BMI >30 may have different PK parameters, but overall the demographics were comparable.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Part A:
At Baseline, 26 of the 28 subjects (92.9%) had at least 1 target joint for bleeds. The median number of target joints was 2 (maximum: 4). There was a high variability among the subjects regarding the number of bleeds in the previous 12 months before enrollment, as the median number of bleeds in the last 12 months was markedly higher in subjects treated on-demand than in subjects on prophylaxis treatment.

Part B:
At Baseline, 44 of the 62 subjects (71.0%) had at least 1 target joint for bleeds; 3 of these subjects with target joints were children. The median number of target joints in the whole Part B population was 1 (maximum: 5). Overall, the median number of bleeds in the previous 12 months was 5.5 and ranged between 0 and 55 bleeds, mostly joint bleeds. None of the children, but 23.1% of the adults was on on-demand treatment at the time of enrollment.

In addition to the disease characteristics, the Gilbert Score* was evaluated in all subjects participating in Part B, and all subjects participating in Part C. The data show that the mean total Gilbert Score was 19.6 ± 13.7 points and ranged between 0 and 51 points. The mean Gilbert Score was 13.6 ± 10.9 points and ranged between 0 and 38 points. There were no relevant differences between the 2 sequence groups.

*The Gilbert score or the World Federation of Hemophilia Physical Examination Score measures joint health of the knees, ankles, and elbows. It is primarily designed for those with established arthropathy.

6.1.10.1.3 Subject Disposition
A total of thirty-one subjects were enrolled in Part A (PK part) of the study, and 28 of these subjects were randomized in equal numbers to the two treatment sequence groups All subjects completed the PK evaluations with both drugs (KOVALTRY and Kogenate FS), and 11 subjects in each sequence group signed the informed consent form for continuation in Part B (prophylaxis treatment with BAY 81-8973). Nineteen of these subjects also completed Part B and underwent valid long-term PK evaluations during Part B.

The total number of subjects enrolled in Part B (including 22 subjects who had already participated in Part A) was 67. Four of them were screening failures, thus, 63 were randomized to treatment with KOVALTRY (31 to the sequence of potency assignment CS/EP → CS/ADJ, and 32 to the sequence CS/ADJ → CS/EP). One subject in the CS/EP → CS/ADJ group withdrew his consent before administration of first dose and 1 further subject discontinued before completion of the first 6-months period (CS/EP). Consequently, 29 of the 31 subjects of the CS/EP → CS/ADJ group and all of the 32 subjects of the CS/ADJ → CS/EP group completed both periods of Part B.

Three subjects of Part B underwent major surgeries during the extension period. A further 6 subjects were enrolled in Part C; 1 was a screening failure and 5 received treatment with KOVALTRY for major surgeries.

Reviewer Comment
The subject in Part B who discontinued was due to a randomization error and the subject never took the study drug. Three of the screening failures had their consent withdrawn. Four had protocol violations including two that did not meet the inclusion criteria. Those with protocol violations were not included in the analysis of efficacy, as they never received study drug. Only four subjects were enrolled in Part C. One subject was enrolled twice for 2 major surgeries and was handled like 2 independent subjects.

6.1.11 Efficacy Analyses

The intent to treat population was used for the primary efficacy analysis which consisted of 62 subjects treated with KOVALTRY in Part B of the study.
All of them had data for the period with potency assignment with CS/EP. One subject randomized to the sequence CS/EP → CS/ADJ terminated the study during the first 6-month treatment period (using CS/EP potency assignment). Therefore, only 61 subjects had data for the period with potency assignment using CS/ADJ. Eighteen subjects were assigned a 2x/week prophylaxis regimen and 44 subjects a 3x/week prophylaxis regimen that was chosen by the investigator.

6.1.11.1 Analyses of Primary Endpoint(s)

Part A:
The primary objective was to demonstrate non-inferiority of KOVALTRY as compared to Kogenate FS. Despite some numerical differences between the results for the PK parameters calculated with the FVIII concentration data from the one-stage and the chromogenic assays, both analyses revealed that the bioavailability of BAY 81-8973 was at least non-inferior to that of Kogenate FS. The median times to achieve maximum plasma concentrations (t_{max}) were 0.42 h or 25 min post-injection (one-stage assay) and 0.67 h or 40 min post-injection (chromogenic assay) for both drugs. Based on the one-stage clotting (OC) assay and the chromogenic substrate (CS) assay, the 90% CIs for the ratio Kovaltry/ Kogenate FS of Cmax 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.

Part B:
The primary efficacy variable was the sum of the annualized number of spontaneous and traumatic bleeds, untreated bleeds, and bleeds with missing reason. During the whole treatment period (CS/EP and CS/ADJ combined), 45 of the 62 subjects of the ITT population experienced a total of 236 bleeds (108 during the CS/EP period and 128 during the CS/ADJ period. The mean and median individually annualized numbers of total bleeds in the whole ITT population was **3.8 ± 5.2 bleeds/year** and **1.0 bleeds/year,** respectively.

	CS/EP (N = 62)	CS/ADJ (N = 61)	Combined (N = 62)
No. of total bleeds			
n	62	61	62
Mean ± SD	1.7 ± 2.6	2.1 ± 3.2	3.8 ± 5.2
Median	1.0	1.0	1.0
[Q1; Q3]	[0.0; 2.0]	[0.0; 4.0]	[0.0; 5.0]
Sum	108	128	236
No. of total bleeds per year			
n	62	61	62
Mean ± SD	3.46 ± 5.28	4.11 ± 6.17	3.79 ± 5.21
Median	1.91	1.88	1.03
[Q1; Q3]	[0.00; 4.37]	[0.00; 7.34]	[0.00; 5.09]

a "Total bleeds" include spontaneous, trauma, untreated bleeds and bleeds with missing reason.
CS/EP = 6-month treatment period using drug with potency assignment by CS/EP.
CS/ADJ = 6-month treatment period using drug with potency assignment by CS/ADJ
Source: BLA 125574/0 CSR 12954 Table 9-1

There was no difference between the bleeding rates during the two different potency periods, but the bleeding rates were higher during the first 6 months in the study than during the second 6 months (median: 2.0 bleeds/year versus 0.0 bleeds/year). The results of the subgroup analysis showed that the median annualized bleeding rate (total bleeds) was higher in children than in adults (median: 2.83 bleeds/year vs. 1.02 bleeds/year), but in contrast to the adults, most of the bleeds in children (69.7%) were trauma bleeds.

A summary of the characteristics bleeds is below:

	CS/EP (N = 111)	CS/ADJ (N = 130)	Total (N = 241)
Reason for 1st injection [n (%)] [a]			
Missing	4 (3.6)	0 (0.0)	4 (1.7)
Spontaneous bleed	64 (57.7)	89 (68.5)	153 (63.5)
Trauma bleed	40 (36.0)	39 (30.0)	79 (32.8)
Other	3 (2.7)	2 (1.5)	5 (2.1)
Bleeding type [n (%)]			
Joint	87 (78.4)	104 (80.0)	191 (79.3)
Muscle	12 (10.8)	7 (5.4)	19 (7.9)
Skin/mucosa	6 (5.4)	10 (7.7)	16 (6.6)
Internal	0 (0.0)	1 (0.8)	1 (0.4)
Other	6 (5.4)	8 (6.2)	14 (5.8)
Bleeding severity [n (%)]			
Mild	59 (53.2)	64 (49.2)	123 (51.0)
Moderate	38 (34.2)	54 (41.5)	92 (38.2)
Severe	14 (12.6)	12 (9.2)	26 (10.8)

Source: BLA 125574/0 CSR 12954 Amendment 2 Table 9-5

There were no relevant differences between the two potency assignment periods, neither with regard to bleeding type nor with regard to their severity. The highest number of joint bleeds in total (n=191 in total) occurred in the knee (n=64 or 33.5%), followed by ankle (n=57 or 29.8%) and elbow (n=54 or 28.3%). Other joints were affected in single cases only. The joints most frequently affected by bleeds in children were the ankles (35.8% of all bleeds) followed by the knees (34.0% of all bleeds).

Reviewer Comment

These data suggest that since there was no difference in the ABR for the two potency dosages, although we do note that the percentage of spontaneous bleeds is higher in the one stage population, as was noted in the Leopold II study. Although the actual number was higher, the ABR was for spontaneous bleeds was comparable with an ABR of 2.0±3.6 (3.4±6.9-Leopold II) dosed via the chromogenic assay versus 2.9±4.6 (3.7 ± 6.3- Leopold II) dosed using the one-stage.

The results show the chromogenic assay could be used to dose subjects without any change in clinical outcome, even though the amount of FVIII measured would be decreased when dosed via this assay. Although, in this cohort of subjects, there is no clinical significance, this could have some impact on particular subjects who are potentially receiving less FVIII due to a bleed.

*The ABR results from Part B of this trial is decreased from the mean ABR calculated in the 12 months prior to the study (11.5 ±15.1**)**, where subjects were on prophylaxis or on-demand therapy. The characteristics and the type of the bleed are typical for this disease process and are expected results.*

Part C:

Eight major surgeries for which BAY 81-8973 was used for hemostatic control were performed in 7 subjects during the study (3 during the extension of Part B and 5 during Part C). One subject was enrolled for surgery twice. Major surgery was defined as any surgical procedure (elective or emergent) that involved general anesthesia and/or respiratory assistance in which a major body cavity was penetrated or exposed, or a substantial impairment of physical or physiological functions was produced. All surgeries were elective. Five of these surgeries were orthopedic surgeries. The hemostatic control was assessed by the surgeons as good or excellent in all cases. However, two subjects had documented blood loss of ≥1L required blood transfusion (1L for one subject during evacuation of a pseudotumor and 2.2 L during implantation of a knee prosthesis). Both subjects required blood transfusions.

Reviewer Comment

There was no pre-specified expected blood loss that was required to be documented prior to surgery as a part of this study protocol. The perioperative data was captured and evaluated by the data monitoring committee. It is unclear how the surgeons assessed hemostasis in the 2 cases of increased blood loss post receiving transfusions, but were assessed as having the expected range of blood loss based on the type of surgery In the case of the knee prosthesis surgery, the amount of blood measured was from a 24 hour drain which included not only blood but also other fluid, which attributed to the high documented blood loss. These two surgeries account for 25% of the major surgeries done in this trial. It is understandable that these major high risk surgeries would have increased blood loss and increased dosages of FVIII used to control bleeding.

6.1.11.2 Analyses of Secondary Endpoints

Part A:

For both drugs (Kogenate and KOVALTRY), mean AUC, $t_{1/2}$ were markedly lower, indicating a higher FVIII clearance in children. However, also in the subgroup of children, the PK parameters were more favorable indicating a slower clearance after injection of KOVALTRY as compared to Kogenate. Repeated PK measurements after 6 to 12 months of prophylaxis treatment with KOVALTRY did not indicate any relevant changes in PK characteristics after long-term treatment.

Part B:

A total of 484 KOVALTRY injections were administered for the treatment of the 241 bleeds; 172 injections were administered for the 111 bleeds during the CS/EP period and 312 injections were administered for the 130 bleeds during the CS/ADJ period. All bleeds were successfully treated with ≤ 2 injections of KOVALTRY. The mean time between the last prophylaxis injection and the occurrence of a bleed (including trauma bleeds) was 1.94 ± 1.26 days, which was in most cases (70.0%) 1-3 days from the previous prophylaxis injection. Subjects were asked to assess the response to treatment of bleeds and done in 235 of the 241 bleeds in total. The response was assessed as “good” or “excellent” in 80.9% of the cases.

Assessment of response to treatment of bleeds was as follows:
Excellent: Abrupt pain relief and/or improvement in signs of bleeding with no additional infusion administered; Good: Definite pain relief and/or improvement in signs of bleeding but possibly requiring more than one infusion for complete resolution; Moderate: Probable or slight improvement in signs of bleeding with at least one additional infusion

for complete resolution; Poor: No improvement at all between infusions or condition worsens.

In vivo recovery values were calculated from the PK data obtained in Part A, the main recovery study was performed in the larger subject population in Part B. The mean *in vivo* recovery values calculated from the FVIII data of Part A (chromogenic assay) were 2.4 ± 0.6 kg/dL for KOVALTRY and 2.5 ± 0.6 kg/dL for Kogenate FS. The corresponding values using the one-stage assay were 1.8 ± 0.4 kg/dL and 1.9 ± 0.4 kg/dL, respectively. Based on the pre- and post-injection FVIII levels determined with the chromogenic assay using the recombinant standard, mean *in vivo* recovery values with CS/EP potency assignment were approximately 2.4 kg/dL, which were approximately 20% lower than with CS/ADJ potency assignment (2.9 - 3.0 kg/dL). There were no relevant differences between the *in vivo* recovery values at start and at mid/end of the respective periods.

FVIII trough levels were measured at each clinic visit prior to the KOVALTRY injection for the measurement of recovery. Comparison of the FVIII trough levels in the subgroups of subjects receiving injections twice per week and those receiving injections three times per week showed that a greater proportion of subjects with higher trough levels received injections3 times per week, especially when determined within 61-84 h after the last dose.

Fourteen subjects underwent a total of 19 minor surgeries in this study and extension. One dose of KOVALTRY was sufficient for 13 of the 16 surgeries, with follow up injections administered for the other three surgeries (13 injections over 8 days in a radiosynoviorthesis, 5 injections over 2 days for a circumcision, 2 injections over 2 days for a dental extraction). Hemostasis was assessed as excellent or good in all cases. No subjects required any blood transfusions.

6.1.11.3 Subpopulation Analyses

The median annualized bleeding rate in children (12-17 years) was 2.83 bleeds/year and in adults 1.02 bleeds/year. This difference was mainly a result of a higher number of trauma bleeds in children (a total of 46 trauma bleeds in the 10 children or on average 4.6 bleeds per subject) than in adults (a total of 33 trauma bleeds in the 52 adults or on average 0.6 bleeds per subject. In both groups, approximately 1/3 of the subjects did not experience any bleeds during Part B. Overall, most of the bleeds in children (69.7% of all bleeds) were trauma bleeds, whereas adult subjects primarily experienced spontaneous bleeds (78.9% of all bleeds). No relevant differences between these 2 subgroups were seen with regard to bleeding type, bleeding severity or the interval between a previous prophylaxis injection and the occurrence of a bleed.

During Part B, 18 subjects used a 2x/week prophylaxis regimen and 44 subjects used a 3x/week prophylaxis regimen. The median dose used for 2x/week prophylaxis regimen was 25.9 IU/kg/injection and 29.2 IU/kg/injection for the 3x/week prophylaxis regimen. Evaluation of the influence of injection frequency (2x/week or 3x/week) did not show any remarkable differences between these two subgroups. There were 52.9% spontaneous bleeds in the 2x/week prophylaxis group and 71.1% spontaneous bleeds in the 3x/week group. In the proportion of trauma bleeds there was also a difference: 47.1% in the subgroup 2x/week vs. 25.7% in the subgroup 3x/week. The time to bleed since previous prophylaxis injection was longer in the 2x/week subgroup in which >60% of bleeds occurred ≥ 2days after the injection.

Reviewer Comment
The subgroup analysis showed that the ABR for the lower frequency regimen was less than the higher frequency ABR (1vs2). Since the frequency regimen was assigned by the investigator, the lower frequency regimen was assigned to individuals with a lower bleeding phenotype which could result in a lower ABR. There were more spontaneous bleeds in the higher frequency group, which is odd since these subjects were dosed more frequently and at a higher median dose, but were noted to be those subjects with an increased bleeding profile. The proportion of trauma bleeds were almost twice in the 2x/week dosing regimen, which may be due to greater number of children in this dosing regimen who are at increased risk for trauma bleeds. Also if these patients had a decreased bleeding phenotype, they may have taken more risks while on a prophylaxis regimen, increasing their traumatic bleed rate. This trial's differences in frequency were further parsed in Leopold II, where the different dosage assignments were also given to the two prophylaxis regimens.

6.1.11.4 Dropouts and/or Discontinuations

There were 7 screening failures. Three of these had their consent withdrawn and four had a protocol violation including 2 where the inclusion criteria were not met. There were five discontinuations in the trial and extension period due to randomization that occurred in error (patient never took study drug), withdrawn consent, and adverse event, noncompliance with study drug, and investigator decision. There were no discontinuations due to SAEs.

Reviewer Comment
The investigator withdrew one subject prior to a planned orthopedic surgery. This subject had been on the study drug for only 3 months. Since only one subject was withdrawn, there is not a significant change in the data. However, this data would have changed how many surgeries would be assessed. It could be possible that this subject was removed so the bleeding assessment perioperatively would not show a poor outcome.

6.1.11.5 Exploratory and Post Hoc Analyses

Comparison within subject to pre-study bleeding rate and on-study bleeding rate was not pre-planned in the protocol.

6.1.12 Safety Analyses

All subjects who received at least one dose of Kogenate FS were included in the safety analysis which applied to 29 subjects in Part A, 62 subjects in Part B (22 from Part A), and 5 subjects in Part C. With the exception of the subject who discontinued during the first period of B, all subjects accumulated at least 50EDs to KOVALTRY by the end of Part B.

6.1.12.1 Methods

All subjects who received at least one dose of KOVALTRY were included in the safety analysis. AEs were assessed in terms of their seriousness, severity, and relationship to study drug. Factors to be considered when associating the use of study drug and AE were: temporal sequence from drug administration, recovery on discontinuation or

recurrence on reintroduction, underlying disease, concomitant medication and pharmacology of the drug.

6.1.12.2 Overview of Adverse Events

There were no deaths in this study (Part A, B, or C). There were no dropouts due to SAEs. The AEs experienced during the study were mostly mild and unrelated to the treatment with KOVALTRY. The most common AEs referred to “infections and infestations”, such as nasopharyngitis, which was reported in approximately 20% of the subjects. Nine AEs in 4 subjects were rated as drug-related, and all of them are also known to occur with Kogenate. Seven SAEs occurred, of which 4 were treatment-emergent. None of the SAEs was rated as drug-related and all subjects recovered.

Part A:
Seven of the 28 subjects experienced at least one treatment-emergent AR. None of the AEs was serious or led to discontinuation from the study. Three non-serious AEs which occurred in 2 subjects were drug related and resolved (paresthesia’s post Kogenate FS period and monocytosis during KOVALTRY; monocytosis during Kogenate FS).

Number of subjects with at least one adverse event	Kogenate FS N = 28 n (%)	BAY 81-8973 N = 27 n (%)	Combined N = 28 n (%)
Any adverse event	5 (17.9) [a]	3 (11.1)	7 (25.0)
Any drug-related AE	2 (7.1)	1 (3.7)	2 (7.1)
Maximum intensity: mild	5 (17.9)	3 (11.1)	7 (25.0)
Any SAE	0 (0.0)	0 (0.0)	0 (0.0)
Any drug-related SAE	0 (0.0)	0 (0.0)	0 (0.0)
AE-related death	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation due to (S)AE	0 (0.0)	0 (0.0)	0 (0.0)

[a] Underlined number changed in CSR Amendment 2 (17.1 changed to 17.9).
Source: BLA 125574/0 CSR 12954 Table 10-2

Reviewer Comment
The three non- serious AEs occurring in 2 subjects were judged to be drug related as they occurred after administration of the drug and in follow ups related to the drug. There was no other relevant history given to attribute these AEs to another cause.

Part B:

Forty-seven subjects experienced at least one treatment emergent AE during the one year prophylaxis treatment in Part B. In two subjects at least 1 AE was rated as severe (1 case of severe ligament sprain and 1case of severe arthralgia, arthritis). None of the AEs led to discontinuation of study drug.

Number of subjects with at least one adverse event	CS/EP N = 62 n (%)	CS/ADJ N = 61 n (%)	Combined N = 62 n (%)
Any adverse event	36 (58.1)	39 (63.9)	47 (75.8)
Any drug-related AE	1 (1.6)	3 (4.9)	4 (6.5)
Maximum intensity: mild	24 (38.7)	27 (44.3)	29 (46.8)
moderate	11 (17.7)	11 (18.0)	16 (25.8)
severe	1 (1.6)	1 (1.6)	2 (3.2)
Any SAE	0 (0.0)	3 (4.9)	3 (4.8)
Any drug-related SAE	0 (0.0)	0 (0.0)	0 (0.0)
AE-related death	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation due to (S)AE	0 (0.0)	0 (0.0)	0 (0.0)

Source: BLA 125574/0 CSR 12954 Table 10-3

Part C:

Four of the five subjects experienced at least one AE. None of the AEs led to discontinuation of study drug.

Number of subjects with at least one adverse event		Total N = 5 n (%)
Any adverse event		4 (80)
Any drug-related AE		0 (0)
Maximum intensity:	mild	2 (40)
	moderate	2 (40)
Any SAE		1 (20)
Any drug-related SAE		0 (0)
AE-related death		0 (0)
Discontinuation due to (S)AE		0 (0)

Source: BLA 125574/0 CSR 12954 Table 10-4

No subjects had a positive FVIII inhibitor level during this part of the study.

There were 2 subjects with seroconversions regarding anti-HSP70 antibody status:

1) Positive anti HSP70 antibody status before entering Part B and subsequent measurements were negative.
2) Negative status during Part A; positive at Month 3 of Part B, and decreased. The transient increase without any clinical symptomatology.

Two subjects tested postive to anti-BHK/HCP antibodies and antibody status did not change during study. One of the subjects became transiently negative and then returned to testing positive.

Reviewer Comment

The relevance of these antibodies is unknown. These subjects did not have any clinical sequelae attributed to the formation of these antibodies which are therefore considered a low risk. The bleeding rates of these subjects were no different from subjects who did not have these antibodies.

6.1.12.3 Deaths

There were no deaths during the study (part A, B, or C).

6.1.12.4 Nonfatal Serious Adverse Events

Six subjects experienced at least one SAE: one subject in Part A; 1 subject during screening in Part B; 3 subjects during treatment in Part B; 1 subject during treatment in Part C. None of the SAEs were drug related and improved/resolved.

Time	SID	Age (years)	Preferred term (MedDRA v. 15.0)	Severity	Treatment-emergent?	Drug-related?	Outcome
Part A	(b) (6)	37	Haematuria	mild	no	no	resolved
		37	Pneumonia	mild	no	no	resolved
Part B		14	Haemarthrosis	mild	no	no	improved
		16	Cephalhaematoma	moderate	yes	no	resolved
		51	Erysipelas	moderate	yes	no	resolved
		51	Chest pain	moderate	yes	no	resolved
Part C		37	Ascites	moderate	yes	no	resolved

Source: CSR 12954 Amendment 2 Table 10-9

Reviewer Comment
These serious AEs were judged to not be drug related as there was no temporal relationship nor causative relationship between administration of drug and SAE.

6.1.12.5 Adverse Events of Special Interest (AESI)

Reviewers are encouraged to exercise clinical judgment in identifying AEs of special interest for particular products. Some of CBER Offices' clinical groups have developed lists of AESIs specific for certain classes of products or adjuvants; check with colleagues and supervisors.

Examples include thromboembolic events in FVII studies, neoantigenicity with FVIII products, autoimmune diagnoses made after receipt of products containing novel adjuvants, and cardiac perforation following intramyocardial catheter delivery of stem cells using a percutaneous catheter.

There was one case of a suspected unexpected serious adverse reaction (SUSAR), which occurred soon after the subject had entered the extension period. Approximately 1 month after entering the extension period and 13 months after starting treatment with KOVALTRY he experienced a severe myocardial infarction 4 h after the KOVALTRY injection. Treatment with KOVALTRY was permanently discontinued.

Reviewer Comment
The subject was 62 years of age and had multiple comorbidities which increased his risk of MI, but KOVALTRY may have had a contributory action since it occurred 4 hours after the infusion and the angiogram showed a clot in in the mid right coronary artery. The subject's event resolved.

6.1.12.6 Clinical Test Results

Identify and discuss treatment-emergent laboratory or vital sign abnormalities (regardless of whether reported as AEs).

Laboratory results showed that less than 10% of the subjects had shifts from high/normal values to values below the lower limit of normal. One of these shifts was reported as an AE (hypokalemia). Review of this was not assessed as drug related due to the temporal nature of this AE and infusion of drug. Shifts from low/normal values at Baseline to values above the upper limit of normal were most frequently seen for (non-fasting) glucose (51.2%), SGPT/ALT (27.9%), SGOT/AST (14.6%) and GGT (11.5%). The only shift to a high abnormality in a laboratory value reported as an AE was "blood creatinine increased".

Reviewer Comment
None of these shifts is clinically relevant, and none of these shifts was reported as an AE. The increase in creatinine was a transient increase decreased to the normal range in subsequent measurements. There were no clusters of events identified.

6.1.12.7 Dropouts and/or Discontinuations

Please refer to the detailed paragraphs above.

6.1.13 Study Summary and Conclusions

The overall conclusions for this study are the following:
The PK profile was not inferior to Kogenate. This trial supported KOVALTRY being efficacious for bleeds. This study showed ABR rates were decreased when switched to prophylaxis for those who were on an on-demand regimen prior to starting the trial that supported the indication for routine prophylaxis. This trial also supports the indication of perioperative management of bleeding as KOVALTRY demonstrated hemostatic efficacy in major and minor surgeries. KOVALTRY was shown to exhibit a good safety profile and did not cause any new or unknown side effects. Moreover, there was no clustering of AES or SAEs. There was no immunogenicity detectable.

6.2 Trial #2

Protocol 12954- Leopold II

Phase 2/3 randomized, cross over, open label trial to demonstrate superiority of prophylaxis over on-demand therapy in PTPs with severe Hemophilia A treated with KOVALTRY.

6.2.1 Objectives (Primary, Secondary, etc)

Primary:
1) To demonstrate the superiority of prophylaxis over on-demand therapy by a clinically significant decrease in bleeding rate following 12 months of treatment with KOVALTRY.

Secondary:
1) To demonstrate superiority of prophylaxis versus on-demand treatment (dose determined by CS/EP and CS/ADJ) as measured by bleeding rate.
2) To determine the non-inferiority of KOVALTRY dose determined by CS/EP vs. CS/ADJ as measured by the proportion of bleeds controlled by ≤ 2 injections in subjects treated on demand.

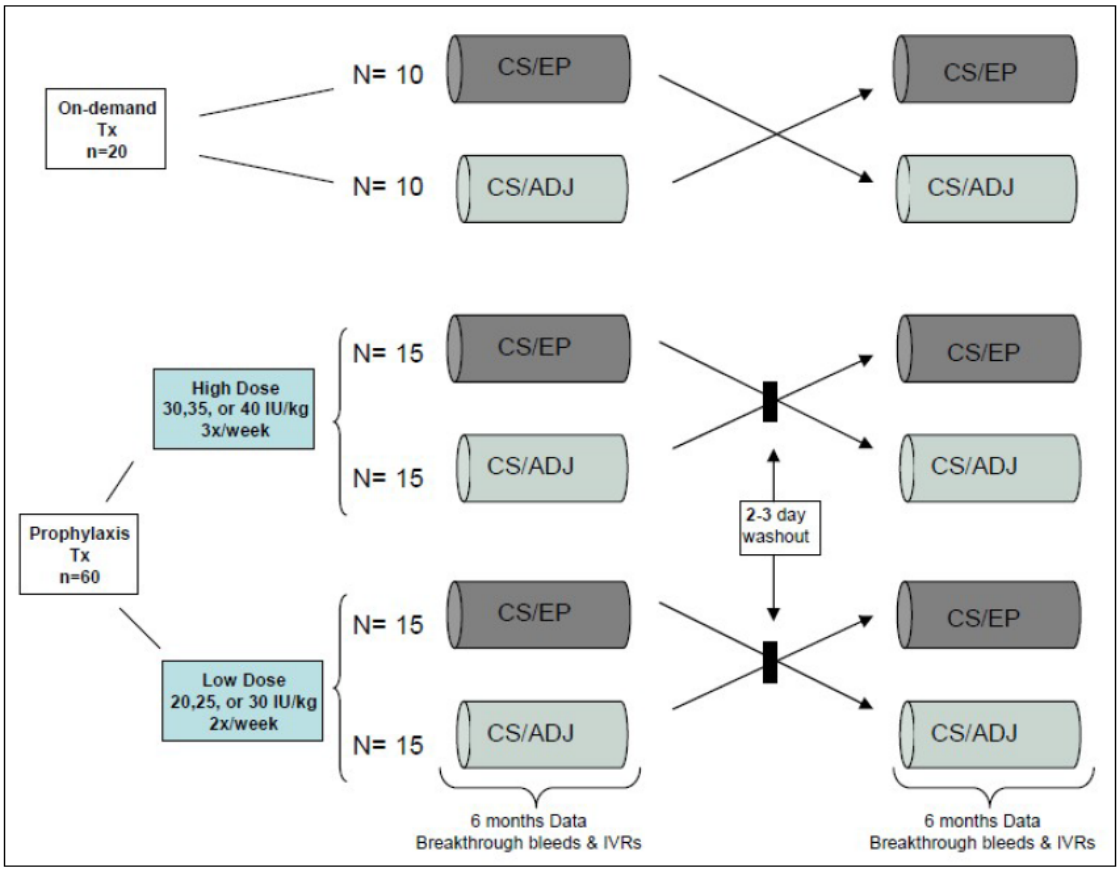
Exploratory:
1) To compare bleeding frequency during prophylaxis treatment with KOVALTRY (CS/EP dose vs. CS/ADJ dose) as measured by the bleeding rate in this study.
2) To compare bleeding frequency during prophylaxis treatment with KOVALTRY (Low dose vs. high dose) as measured by bleeding rate in this study.
3) 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 KOVALTRY.
4) To assess the safety and tolerability profile of KOVALTRY (during prophylaxis and on demand treatment), by assessing clinical chemistry, hematological parameters, and adverse event presentation.
5) To evaluate the potential for antibody formation to heat shock protein-70 (HSP-70) and/or hamster proteins during KOVALTRY treatment.
6) To evaluate the potential for inhibitory antibody formation to KOVALTRY during study treatment.
7) To evaluate all surgical outcomes during treatment with KOVALTRY.
8) To assess health-related quality of life (HRQoL) and pharmacoeconomic parameters during treatment with KOVALTRY.

6.2.2 Design Overview

Randomized, multicenter, open label study with intra-individual cross-over between 2 potency periods.
Low-dose prophylaxis: 20, 25 or 30 IU/kg, 2x/week.
High-dose prophylaxis: 30, 35 or 40 IU/kg, 3x/week.

Subjects were to be randomized to 1 of 6 treatment arms:
1. On-demand treatment: Sequence CS/EP → CS/ADJ
2. On-demand treatment: Sequence CS/ADJ → CS/EP
3. Low-dose prophylaxis: Sequence CS/EP → CS/ADJ
4. Low-dose prophylaxis: Sequence CS/ADJ → CS/EP
5. High-dose prophylaxis: Sequence CS/EP → CS/ADJ
6. High-dose prophylaxis: Sequence CS/ADJ → CS/EP

All subjects in the 6 arms were to undergo either prophylaxis or on-demand treatment for a period of 6-months. After a 2-3-day washout period (for the prophylaxis subjects), subjects were to be crossed-over (within their respective treatment groups) to the alternate treatment arm (potency assignment of KOVALTRY as determined by either CS/EP or CS/ADJ) for a further 6-month treatment period.



CS/ADJ = Chromogenic substrate assay/label adjusted to mimick one-stage assay;
CS/EP = Chromogenic assay per European Pharmacopoeia;
IVR = *In vivo* recovery
Tx = Treatment

Source: BLA 125574/0 CSR 14319 Figure 7-1

Reviewer Comment
The dosage for prophylaxis was dosed at a lower dose with less frequency and at a higher dose with increased frequency where one would expect greater efficacy in the regimen dosed more frequently with higher doses. Once assigned, this was to be maintained for the duration of the trial. Subjects were allowed to be given extra doses for breakthrough bleeds and the dose could have been increased if the subject was experiencing more bleeds (within the dosing cohort).

6.2.3 Population

The following criteria were used to evaluate subjects for inclusion in the study:
1. Male, aged 12 to 65 years
2. Severe hemophilia A, defined as < 1% FVIII:C as determined by one-stage clotting assay at the time of screening. If screening result turned out to be equal to or higher than 1%, then severe hemophilia A could be confirmed by one of the following:
a. Documented historical evidence from a recognized (certified) clinical laboratory (acceptable to Global Clinical Lead) demonstrating < 1% FVIII:C as determined by one-stage clotting assay.
b. Assay results from a previous Bayer hemophilia clinical trial.
3. ≥150 exposure days (ED) in total with any recombinant FVIII or plasma-derived FVIII only. Cryoprecipitate and fresh frozen plasma treatments were not considered in this total.
4. Currently receiving episodic treatment with FVIII; and no regular prophylaxis for >6 consecutive months in the previous 5 years.
5. No current evidence of inhibitor antibody as measured by the Nijmegen-modified Bethesda assay [<0.3 Bethesda units per mL (BU/mL)] in 2 consecutive samples and absence of clinical signs or symptoms of decreased response to FVIII administration. (First negative sample could be historical if obtained within 3 months prior to screening with a result of 0.6 BU/mL by a classical Bethesda assay. The testing for a second negative, confirmatory sample was to be, in all cases, performed by a central laboratory using the Nijmegen test. If a first recent sample was not available, then testing for 2 negative samples were to be performed by the central laboratory at least 1 week apart). Subjects were not to receive FVIII within 72 h prior to the collection of samples for inhibitor testing. The time period since the last FVIII injection was not to be longer than 4 weeks.
6. No history of FVIII inhibitor formation defined as inhibitor antibody <0.6 BU/mL by the Nijmegen-modified or classical Bethesda assay. However, subjects with a maximum historical titer of 1.0 BU with the Classical Bethesda assay on no more than 1 occasion but with at least 3 subsequent successive negative results (<0.6 BU) thereafter were also eligible.
7. Willingness and ability to complete training in the use of the study electronic patient diary (EPD) by the subject or a surrogate (a caregiver or family member over 18 years of age).
8. Written informed consent by subject and parent/legal representative, if under age of consent per local regulation.

The following criteria were used for the exclusion of subjects from the study:
1. Presence of another bleeding disease that is different from hemophilia A (*eg*, von Willebrand disease, hemophilia B).
2. Thrombocytopenia (platelet count < 100 000/mm3).

3. Abnormal renal function (serum creatinine > 2.0 mg/dL).
4. Presence of active liver disease verified by medical history or persistent and increased alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5x the upper limit of normal (ULN) or severe liver disease as evidenced by an international normalized ratio (INR) >4, hypoalbuminemia, and portal vein hypertension.
5. Received treatment with immunomodulatory agents within the last 3 months prior to study entry or requires treatment during the study. [The following drugs were allowed: interferon-α treatment for hepatitis C virus (HCV), highly active antiretroviral therapy (HAART) for human immunodeficiency virus (HIV), and or a total of 2 courses of pulse treatment with steroids for a maximum of 7 days at 1 mg/kg or less].
6. Absolute CD4 lymphocyte cell count < 250 cells/L.
7. Receiving or has received other experimental drugs within 3 months prior to study entry, with the exception of Kogenate FS/Bayer (Bayer factor VIII study drugs) received in studies within 2 weeks prior to study entry.
8. Requires any pre-medication to tolerate FVIII injections (*eg*, antihistamines).
9. Unwilling to comply with study visits or other protocol requirements or not suitable for participation in this study for any reason, according to the Investigator.
10. Known hypersensitivity to hamster and / or mouse protein.
11. Known hypersensitivity to the components in this product.
12. Any subject who cannot forego 2-3 days without receiving FVIII for washout purposes.

Reviewer Comment
The inclusion and exclusion criteria are acceptable.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Route of administration: Manual IV injection over 1 – 15 minutes
Dosage for prophylaxis treatment: Low-dose group: 20, 25 or 30 IU/kg, 2x/week
High-dose group: 30, 35 or 40 IU/kg, 3x/week
Dosage for on-demand treatment: The dosage was to be adjusted to bleeding location and severity and to current standard care.
Duration: 12 months

6.2.5 Directions for Use

No directions for use were provided in the study protocol for review.

6.2.6 Sites and Centers

There were 31 subjects enrolled in China, 2 subjects enrolled in the Czech Republic, 9 subjects enrolled in Japan, 9 subjects enrolled in Mexico, 18 subject enrolled in Romania, 5 subjects enrolled in the Republic of Serbia, 7 subjects enrolled in Russia, 5 subjects enrolled in Turkey, 3 subject enrolled in Taiwan, 6 subjects enrolled in South Africa, and 2 subjects enrolled in the United States.

6.2.7 Surveillance/Monitoring

The following table shows the monitoring that occurred during the study:

Procedures	Visit 1 Screening/ Baseline (within 6 wks)	Visit 2 Month 0 no later than 6 wks from Visit 1)	Visit 3 Month 3 (± 7 days)	Visit 4 Month 6 End of 6-mo period (± 7 days)	Visit 5 Start of next 6-mo period Cross-Over (± 7 days) a 2-3-day washout)	Visit 6 Month 9 (± 7 days)	Visit 7 Month 12 End of Treatment/ Early Discon-tinuation (± 7 days)	Follow-up Phone Call (1-2 weeks after end of treatment)
Informed consent	X							
Confirm eligibility criteria	X	X						
Medical and disease history	X							
Complete physical exam with weight	X [a]			X			X	
Joint assessment (Gilbert Score)	X							
Haemo-QoL(-A) questionnaire	X	X		X			X	
EQ-5D questionnaire	X	X		X			X	
CD4 cell count	X							
Serology (HIV, HBV, HCV)	X							
FVIII:C level	X							
Lupus anticoagulant antibodies	X							
CBC with differentials, platelets, coagulation	X	X	X	X		X	X	
Serum chemistry including liver enzymes, renal function	X	X	X	X		X	X	
Routine urinalysis	X		X	X		X	X	
Urine by dipstick for hematuria		X [b]		X [b]	X [b]		X [b]	
Inhibitor testing	X		X	X		X	X	
HSP-70 Ab and host cell protein Ab	X		X	X		X	X	
In vivo FVIII recovery/aPTT		X [b]		X [b]	X [b]		X [b]	
Pharmacogenetics	X [f]	X [f]	X [f]	X [f]	X [f]	X [f]	X [f]	
48-hour PK sampling [g]		X						
Vital signs (pulse, BP, resp. rate, temperature (pre- & post-injection)	X [c]	X	X [c]	X	X [b]	X [c]	X	
Administer study medication		X [b]		X [b]	X [b]		X [b,d]	
Electronic patient diary training and review data entry		X	X	X	X [b]	X	X	
Adverse event review	X	X	X	X	X [b]	X	X	X
Concomitant medication review	X	X	X	X	X [b]	X	X	X
Dispense study drug for home		X	X	X [e]	X [b]	X		
Drug accountability		X	X	X	X [b]	X	X	
Follow-up phone call every 2 weeks		X	X	X	X [b]	X	X	

(a) Height is also measured during Visit 1.
(b) For subjects randomized to prophylaxis treatment arm only.
(c) Vital signs done only once at this visit.
(d) Study drug administration may not occur, if subject is discontinued early.
(e) For subjects randomized to the on-demand treatment arm only
(f) A separate informed consent must be signed for pharmacogenetics. A sample for FVIII genetic analysis should be taken preferably at Screening; however, it can also be taken at a later visit, but not later than the last visit.
(g) Blood samples will be collected in Japanese subjects (local Amendment 2)

Source: BLA 125574/0 Study 14319 Table 7-1. Page 22/97

6.2.8 Endpoints and Criteria for Study Success

Primary efficacy variable:
-Annualized bleeding rate (all bleeds)
Other efficacy variables:
-Number of bleeds
-FVIII recovery values
-FVIII usage calculation expressed as number of injections, number of prophylaxis injections
-Description of bleeding according to location and frequency of all bleeds, joint bleeds, spontaneous bleeds, trauma bleeds, and bleeds within 48 h after a prophylaxis injection
-Control of bleeding as measured by the number of injections required to treat a bleed.
-Proportion of bleeds controlled by ≤ 2 injections (among all bleeds) (Note: the protocol specified 1 or 2 injections but should have also included untreated bleeds.)
-Subject's assessment of response to treatment of major bleeds, with the hemostatic outcome of bleeding episodes expressed as "excellent", "good", "moderate" and "poor"
-Hemostatic outcome of surgeries (both major and minor) including blood loss, transfusion, hemostatic-related surgical complications, and assessment of hemostasis
-Change in HRQoL (as assessed by Haemo-QoL-A questionnaire and EQ-5D Health Questionnaire)

6.2.9 Statistical Considerations & Statistical Analysis Plan

The ITT population was to be used for the primary efficacy analysis.

Statistical methodology:
An ANOVA model with effect for treatment group was planned for the primary efficacy endpoint, as well as for the secondary efficacy endpoints of ABR for the individual potency assignments. Poisson regression was used for the primary sensitivity analysis.

Other efficacy variables and all safety variables were planned to be analyzed using summary statistics.

6.2.10 Study Population and Disposition

Ninety-seven male subjects were enrolled with 14 screening failures. Of the 83 subjects randomized to 1 of 6 treatment arms,three subjects were not treated, thus 80 subjects were included in the ITT population. The following shows the subject disposition:

On-demand CS/EP → CS/ADJ N = 11		On-demand CS/ADJ → CS/EP N = 10		Low-dose prophylaxis CS/EP → CS/ADJ N = 14		Low-dose prophylaxis CS/ADJ → CS/EP N = 16		High-dose prophylaxis CS/EP → CS/ADJ N = 16		High-dose prophylaxis CS/ADJ → CS/EP N = 16	
Not treated:	0	Not treated:	0	Not treated [b]:	1	Not treated [b]:	1	Not treated:	0	Not treated [b]:	1
Treated:	11	Treated:	10	Treated:	13	Treated:	15	Treated:	16	Treated:	15
Early termination [a]:	1	Early termination:	0	Early termination:	0	Early termination:	0	Early termination:	0	Early termination:	0
Completed:	10	Completed:	10	Completed:	13	Completed:	15	Completed:	16	Completed:	15

a Reason for termination: Non-compliance with documentation of dosing.
b Reasons for not being treated: Consent withdrawn (n=2) and protocol violation (n=1).
Source: Original from BLA 125574/0; Clinical Study Report PH37042, V2.0, Figure 8-1

6.2.10.1 Populations Enrolled/Analyzed

The following subjects were analyzed:

Analysis set	On-demand (N = 21)	Low-dose Prophylaxis (N = 28)	High-dose Prophylaxis (N = 31)	Total (N = 80)
Safety population	21	28	31	80
ITT population	21	28	31	80
PP population	20	28	31	79
PK analysis population	1	1	2	4

Source: Original from BLA 125574/0; Clinical Study Report PH37042, V2.0, Table 8-1

Eighty subjects were included in the intent to treat and safety populations. One patient who was treated on demand discontinued the study due to non-compliance with the documentation of dosing; therefore, 79 subjects were valid for per protocol analysis. (ITT population: injection or bleeding data from the electronic patient diary EPD/CRF; PP population: All subjects in ITT population without any protocol deviations and have EPD data from both cross over periods).

6.2.10.1.1 Demographics

The 80 males were aged between 14 and 59 years. Ten subjects were adolescents (14-16 years). The majority were White (45%) or Asian (40%) race. The following table displays the demographic and other baseline characteristics:

	On-demand (N = 21)	Low-dose Prophylaxis (N = 28)	High-dose Prophylaxis (N = 31)	Total (N = 80)
Sex [n (%)]				
Male	21 (100.0)	28 (100.0)	31 (100.0)	80 (100.0)
Race				
White	6 (28.6)	16 (57.1)	14 (45.2)	36 (45.0)
Black	3 (14.3)	0 (0.0)	1 (3.2)	4 (5.0)
Asian	9 (42.9)	9 (32.1)	14 (45.2)	32 (40.0)
Hispanic	3 (14.3)	3 (10.7)	2 (6.5)	8 (10.0)
Age (years)				
n	21	28	31	80
Mean ± SD	31.4 ± 10.9	28.8 ± 10.9	29.1 ± 11.5	29.6 ± 11.0
Median	30.0	27.0	28.0	28.5
[Min; Max]	[14; 53]	[14; 54]	[14; 59]	[14; 59]
Age group [n (%)]				
<18 years	2 (9.5)	4 (14.3)	4 (12.9)	10 (12.5)
18 - <30 years	6 (28.6)	14 (50.0)	12 (38.7)	32 (40.0)
≥30 years	13 (61.9)	10 (35.7)	15 (48.4)	38 (47.5)
Baseline weight (kg)				
n	20	28	31	79
Mean ± SD	69.17 ± 15.96	65.31 ± 14.79	64.63 ± 11.74	66.02 ± 13.94
Median	65.00	65.00	64.00	65.00
[Min; Max]	[45.0; 103.0]	[46.0; 98.0]	[46.0; 88.9]	[45.0; 103.0]
Baseline height (cm)				
n	20	28	31	79
Mean ± SD	172.6 ± 9.8	175.0 ± 6.9	173.2 ± 8.0	173.6 ± 8.1
Median	170.2	173.8	173.0	173.0
[Min; Max]	[156; 192]	[158; 190]	[153; 189]	[153; 192]
Baseline BMI (kg/m^2)				
n	20	28	31	79
Mean ± SD	23.02 ± 3.80	21.33 ± 4.59	21.51 ± 3.33	21.83 ± 3.95
Median	22.65	21.12	21.32	21.63
[Min; Max]	[16.5; 31.7]	[15.0; 30.9]	[17.0; 27.6]	[15.0; 31.7]

Source: Original from BLA 125574/0; Clinical Study Report PH37042, V2.0, Table 8-2

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
79 subjects were confirmed to have severe HA. Seventy-seven subjects had documentations of previous bleeds, with a range of 3-106 bleeds in the previous year. Ninety percent of the subjects had target joints for bleeds. The Gilbert score to evaluate joint was performed at baseline on the enrolled patients and there were no relevant differences among the treatment groups.

	On-demand (N = 21)	Low-dose Prophylaxis (N = 28)	High-dose Prophylaxis (N = 31)	Total (N = 80)
Number of target joints				
n	21	28	30	79
Mean ± SD	3.2 ± 2.0	3.0 ± 2.2	2.8 ± 2.1	3.0 ± 2.1
Median	3.0	3.0	2.0	3.0
[Min; Max]	[0; 9]	[0; 7]	[0; 8]	[0; 9]
No. of bleeds in the last 12 months				
n	21	26	30	77
Mean ± SD	47.5 ± 26.4	38.4 ± 23.3	45.6 ± 29.9	43.7 ± 26.8
Median	41.0	35.0	38.5	36.0
[Min; Max]	[12; 106]	[7; 84]	[3; 106]	[3; 106]
No. of joint bleeds in the last 12 months				
n	21	26	30	77
Mean ± SD	33.5 ± 23.9	30.3 ± 22.5	32.7 ± 25.4	32.1 ± 23.8
Median	28.0	24.0	25.0	24.0
[Min; Max]	[1; 104]	[2; 76]	[3; 95]	[1; 104]

Source: Adapted from BLA 125574/0; Clinical Study Report PH37042, V2.0, Table 8-3

6.2.10.1.3 Subject Disposition
Please refer to Section 6.2.10 above for disposition of the subjects in the study.

6.2.11 Efficacy Analyses

The intent to treat population of 80 subjects was used for the primary efficacy analysis. Subgroups based on age, region, dose, Gilbert score and bleeding frequency were analyzed.

6.2.11.1 Analyses of Primary Endpoint(s)

A total of 1497 bleeds were reported in the ITT population during this study (1204 in the 21 on-demand subjects and 293 in the 59 prophylaxis subjects). The median ABRs were 60 bleeds/year and 1.98 bleeds/year, respectively. Comparison of the ABRs in an ANOVA resulted in $p<0.0001$. The results comparing on-demand treatment versus high and low dose prophylaxis also showed statistical significance, which was verified by the statistical reviewer. The median bleeding rate in the high dose group (1.97) was lower when compared to the low dose group (4.02), which was also significantly different ($p<0.0001$). There was not a statistical difference between the two potency assignments in subjects treated on demand (CS/EP: 28.9 mean total bleeds; CS/ADJ: 29.9 mean total bleeds). Within the 2 prophylaxis groups, there were no differences in the annualized bleeding rates (CS/EP: 2.6 mean total bleeds; CS/ADJ: 2.4 mean total bleeds).

Reviewer Comment
The primary objective was to demonstrate the superiority of prophylaxis over on-demand therapy during the 12 months of treatment. The secondary objective was to show the superiority of the prophylaxis treatment over on-demand treatment for the two potency assignments: CS/EP and CS/ADJ and demonstrate the non-inferiority of CS/EP potency to the CS/ADJ potency. Therefore, the primary and secondary objectives of this study were met.
These results are not surprising as prophylaxis treatment should result in a decreased bleeding rate compared to on demand treatment. It is also not surprising that those dosed with a higher amount and more frequently should also have a lower bleeding rate than those subjects given less and dosed less frequently.

6.2.11.2 Analyses of Secondary Endpoints

See above.

6.2.11.3 Subpopulation Analyses

Age and region subgroup analyses were performed on the primary efficacy variable. Across the subgroups, the ABR during prophylaxis treatment was lower than during on-demand treatment. The median ABR in 18-30 age group was double when compared to the median ABR in ≥30 age group in the prophylaxis treatment (4.5 vs. 2). Asian versus non-Asian did not show a difference in the combined data for prophylaxis, but the on demand median rate was higher in the Asian population.

ABR in Subpopulation Analysis:

	On-demand	Prophylaxis		
	Combined N = 21	Low dose N = 28	High dose N = 31	Combined N = 59
Age group				
Adolescents (14 to 16 years)				
n	2	4	4	8
Mean ± SD	20.13 ± 2.46	5.96 ± 7.24	2.47 ± 1.70	4.22 ± 5.21
Median	20.13	4.03	1.98	1.98
[Min; Max]	[18.4; 21.9]	[0.0; 15.8]	[1.0; 4.9]	[0.0; 15.8]
Adults (≥ 18 years)				
n	19	24	27	51
Mean ± SD	61.65 ± 22.28	5.65 ± 7.31	4.53 ± 6.92	5.06 ± 7.06
Median	61.30	4.02	1.97	1.98
[Min; Max]	[18.2; 101.3]	[0.0; 33.1]	[0.0; 25.9]	[0.0; 33.1]
Adults (18 to < 30 years)				
n	6	14	12	26
Mean ± SD	70.26 ± 24.93	7.55 ± 8.87	6.02 ± 7.34	6.84 ± 8.07
Median	63.13	5.58	3.00	4.53
[Min; Max]	[41.7; 101.3]	[0.0; 33.1]	[0.0; 21.6]	[0.0; 33.1]
Adults (≥ 30 years)				
n	13	10	15	25
Mean ± SD	57.68 ± 20.77	3.01 ± 3.10	3.33 ± 6.58	3.20 ± 5.37
Median	59.96	2.48	1.01	1.96
[Min; Max]	[18.2; 85.5]	[0.0; 8.1]	[0.0; 25.9]	[0.0; 25.9]
Region				
Asia				
n	9	9	14	23
Mean ± SD	66.93 ± 21.71	5.74 ± 4.09	3.59 ± 6.56	4.43 ± 5.72
Median	62.13	5.05	1.97	1.98
[Min; Max]	[37.1; 101.3]	[0.0; 11.8]	[0.0; 21.6]	[0.0; 21.6]
Non-Asia (total)				
n	12	19	17	36
Mean ± SD	50.77 ± 25.13	5.68 ± 8.34	4.81 ± 6.60	5.27 ± 7.48
Median	48.01	2.03	1.97	2.00
[Min; Max]	[18.2; 85.5]	[0.0; 33.1]	[0.0; 25.9]	[0.0; 33.1]
South Africa				
n	4	0	1	1
Mean ± SD	39.86 ± 28.65	-	4.10	4.10
Median	31.22	-	4.10	4.10
[Min; Max]	[18.2; 78.8]	-	[4.1; 4.1]	[4.1; 4.1]
North America				
n	3	4	2	6
Mean ± SD	32.01 ± 9.95	3.46 ± 6.26	0.50 ± 0.71	2.47 ± 5.09
Median	32.42	0.51	0.50	0.50
[Min; Max]	[21.9; 41.7]	[0.0; 12.8]	[0.0; 1.0]	[0.0; 12.8]
Europe				
n	5	15	14	29
Mean ± SD	70.76 ± 13.73	6.27 ± 8.91	5.48 ± 7.09	5.89 ± 7.95
Median	76.32	3.01	2.99	3.01
[Min; Max]	[52.0; 85.5]	[0.0; 33.1]	[0.0; 25.9]	[0.0; 33.1]

Source: Adapted from BLA 125574/0; Clinical Study Report PH37042, V2.0, Table 9-15

Reviewer Comment

The younger adults had a higher median ABR than the older adults. which could be due to increased physical activity, but should also be seen in the on-demand arm. Since these are small sample sizes due to the subgroup analysis, this may be due to chance from multiplicity noncompliance, or having a lower dose given. Of note, the range of the younger adult category is wider in which case, outliers are attributing to the data set. The totality of the data with favorable efficacy outcomes for the low and high dose regimens as compared to the on-demand regimen in the 18-<30 year sub-group, the wide dose range and twice and thrice a week regimen proposed in the package insert and the

comparable ABR rates in the two age sub-groups for on-demand therapy were taken into consideration when concluding that both low and high dose prophylaxis regimens are effective in this young adult sub-group.

6.2.11.4 Dropouts and/or Discontinuations

A total of 97 males were enrolled in this study. Fourteen subjects were screening failures. Two subjects randomized to the low dose treatment and 1 subject randomized to the high dose treatment terminated the study prior to their first dose. A single subject was considered as a non-compliant subject and excluded from the per protocol population.

6.2.11.5 Exploratory and Post Hoc Analyses

None of the subjects in the on demand group remained bleed free during the study, Sixteen subjects in the prophylaxis group remained bleed free during the study.

The median ABR of spontaneous bleeds was 42 bleeds/year in the on-demand group and 1 bleed/year in the prophylaxis group. The median ABR of joint bleeds was also lower in the prophylaxis group versus on-demand (2 versus 39 bleeds/year, respectively).

The median dose per injection was lower in the on-demand group than in prophylaxis

	On-demand	Prophylaxis		
	Combined N = 1204 n (%)	Low dose N = 160 n (%)	High dose N = 133 n (%)	Combined N = 293 n (%)
Bleeding Type [n (%)]				
Missing	2	7	3	10
n	1202 (100.0)	153 (100.0)	130 (100.0)	283 (100.0)
Spontaneous bleed	943 (78.5)	127 (83.0)	82 (63.1)	209 (73.9)
Trauma bleed	258 (21.5)	26 (17.0)	48 (36.9)	74 (26.1)
Other	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Bleeding site [n (%)]				
Missing	7	0	0	0
n	1197 (100.0)	160 (100.0)	133 (100.0)	293 (100.0)
Joint	924 (77.2)	145 (90.6)	110 (82.7)	255 (87.0)
Muscle	179 (15.0)	7 (4.4)	17 (12.8)	24 (8.2)
Skin/mucosa	83 (6.9)	7 (4.4)	3 (2.3)	10 (3.4)
Internal	7 (0.6)	1 (0.6)	1 (0.8)	2 (0.7)
Other	4 (0.3)	0 (0.0)	2 (1.5)	2 (0.7)

group (22.03 [range 11 to 35] vs. 29.41 [range 19 to 49] IU/kg/injection).

Irrespective of the treatment regimen, most of the bleeds were joint bleeds (77.2% in the on- demand group and 87.0% in the prophylaxis group).

A total of 1607 Kovaltry injections were administered for the on-demand group and 3502 for the prophylaxis group. The majority of bleeds were treated with 1 or 2 injections.

	On-demand	Prophylaxis		
	Combined N = 1204	Low dose N = 160	High dose N = 133	Combined N = 293
No. of injections per bleed				
n	1204	160	133	293
Mean ± SD	1.3 ± 1.0	1.2 ± 0.9	1.2 ± 0.5	1.2 ± 0.7
Median	1.0	1.0	1.0	1.0
[Min; Max]	[0; 20]	[0; 7]	[0; 4]	[0; 7]
Sum	1607	198	154	352
No. of bleeds by no. of inj. [n (%)]				
n	1204 (100.0)	160 (100.0)	133 (100.0)	293 (100.0)
≤ 2 injections	1147 (95.3)	152 (95.0)	130 (97.7)	282 (96.2) [a]
Not treated	2 (0.2)	7 (4.4)	1 (0.8)	8 (2.7)
1 injection	909 (75.5)	126 (78.8)	114 (85.7)	240 (81.9)
2 injections	236 (19.6)	19 (11.9)	15 (11.3)	34 (11.6)
3 injections	40 (3.3)	4 (2.5)	2 (1.5)	6 (2.0)
>3 injections	17 (1.4)	4 (2.5)	1 (0.8)	5 (1.7)

[a] Underlined number changed in CSR Amendment 1 (262 changed to 282, 89.4 changed to 96.2).
N/A = not applicable
Source: Adapted from BLA 125574/0; Clinical Study Report PH37042, V2.0, Table 9-4

The response to treatment of bleeds was assessed for 1475 of the 1497 treated bleeds in total. The response was assessed as “good” or “excellent” in 68.2% (1006/1475) of the bleeds.
Source: Original from BLA 125574/0; Clinical Study Report PH37042, V2.0, Table 9-5

6.2.12 Safety Analyses

There were three groups evaluated: on-demand, low dose prophylaxis and high dose prophylaxis. All of the 80 treated subjects were included in the safety population. All but one subject in the on-demand group completed the one year study.

6.2.12.1 Methods

All subjects who received at least one dose of KOVALTRY were included in the safety analysis. AEs were assessed in terms of their seriousness, severity, and relationship to study drug. Factors to be considered when associating the use of study drug and AE were: temporal sequence from drug administration, recovery on discontinuation or recurrence on reintroduction, underlying disease, concomitant medication and pharmacology of the drug.

6.2.12.2 Overview of Adverse Events

There were no deaths in this study. Eighty of the subjects (10%) in the safety population experienced at least 1 AE during the screening period. There were two SAEs. No subjects discontinued the study due to an AE or SAE.

Immunogenicity of KOVALTRY was evaluated with regard to antibody development against FVIII. There were no subjects that developed inhibitory antibodies to FVIII.

Antibody formation of KOVALTRY to HSP-70 and BHK/HCP was also evaluated. Two subjects had positive anti-HSP70 antibody titers at screening and eight subjects in the prophylaxis group became anti-HSP-70 antibody positive during the study. Out of those eight, 5 were antibody negative by the end of the study and the remaining three had decreasing titers. No clinical sequelae were demonstrated in any of these patients.

6.2.12.3 Deaths

There were no deaths in this study.

6.2.12.4 Nonfatal Serious Adverse Events

There were 2 treatment-emergent SAEs including asthma and a head injury which were reported as unrelated to the study drug. Treatment emergent AEs occurred in 44 subjects. The highest incidence of 31.3% was seen in AEs referring to the MedDRA system organ class “infections and infestations”, such as nasopharyngitis (16.3%), upper respiratory tract infection (7.5%) or influenza (5.0%). In 3 subjects, drug-related AEs were assessed as including hypersensitivity reactions, and a transient lymphadenopathy.

Reviewer Comment

There were three SAEs including a head injury, gastric ulcer hemorrhage, and an asthma attack. All three SAEs resolved. The head injury and asthma attack were treatment emergent. The head injury was a traumatic accident that occurred and highly unlikely there is a causal relationship between the study drug and this injury. The asthma attack was precipitated by exposure to cold and rain and had been on the study for two months at that time. There was no temporal relationship between the drug administration and this SAE and is unlikely to be caused by the study drug.

The three AEs that were attributed as drug related were the following: one reported infusion site pruritus which resolved within minutes and likely due to the study drug; the second reported was an allergic dermatitis after the start of treatment which could be due to the study drug; the third AE reported was lymphadenopathy after days of the injection with resolution in thirty minutes. This is an unusual AE to have after an injection but could be from the study drug due to the temporal relationship.

There were no other clusters of AEs that were likely to be drug related.

6.2.12.5 Adverse Events of Special Interest (AESI)

There were no cases of thrombosis in this study.

6.2.12.6 Clinical Test Results

Mean and median changes from Baseline to Months 3, 6, 9 and 12 (or end of treatment) were analyzed. Generally, none of these analyses showed any relevant mean/median changes. Treatment-emergent shifts from high/normal values to values below the lower limit of normal occurred in <11% of the subjects.

Reviewer Comment

None of the shifts in laboratory data were reported as AEs except for 3 events which included increased AST/ALT and total bilirubin. These were transient and judged not likely to be drug related.

6.2.12.7 Dropouts and/or Discontinuations

There were no subjects that discontinued study treatment due to an AE or SAE.

6.2.13 Study Summary and Conclusions

This study included 80 PTPs (10 adolescents) who were either White (45%) or Asian (40%). The objective was to demonstrate superiority of prophylaxis over on demand treatment with KOVALTRY. Subjects were randomized to on-demand treatment, a low dose prophylaxis group, or a high dose prophylaxis group. The median ABR was 60 bleeds/year in the on-demand group and 2 bleeds/year in the combined prophylaxis group. The overall efficacy of KOVALTRY in the treatment of bleeds was further proven as the majority of bleeds was controlled with ≤2 injections and assessed as good or excellent. Treatment with KOVALTRY was also safe and well tolerated with only a few AEs that were drug related and no clustering of AEs which would demonstrate a safety signal.

This trial supports the indication for adults and adolescents for routine prophylaxis and for the treatment and control of bleeds.

6.3 Trial #3

Protocol 13400- Leopold Kids

This study is a multi-center Phase 3 uncontrolled open-label trial to evaluate safety and efficacy of BAY81-8973 in children with severe hemophilia A under prophylaxis therapy.

6.3.1 Objectives (Primary, Secondary, etc)

The primary objective was to evaluate the safety and efficacy of the treatment with KOVALTRY for prophylaxis and treatment of breakthrough bleeds in children with severe Hemophilia A.

The secondary objectives are:
- to assess the safety and efficacy of KOVALTRY during surgeries
- to assess incremental recovery of KOVALTRY
- to assess pharmacokinetic parameters in PTPs and PUPs

6.3.2 Design Overview

The study is divided in two parts:
1) Investigate a total of 50 PTPs ≤12 years of age (Part A)
2) Investigate at least 25 PUPs (ongoing- Part B)

Subjects in Part A were to be treated with 25-50 IU/kg at least 2x/week or more frequently as needed for prophylaxis.
Subjects in Part B were to begin with 15-50 IU/kg for prophylaxis at least 1x/week or the with the subject's first bleeding event. Dose decisions were made at the discretion of the investigator.

Enrollment was staggered. Part A started after 20 adult/adolescents had 50 EDs without safety concerns in previous studies. PTPs 6 to 12 years began enrollment followed by PTPs <6 years. Part B began enrollment after 20 children in Part A accumulated 50 EDs each.

Part A: 50 PTPs; 25 subjects aged >6-12 years; 25 subjects 0-6 years was the initial study goal.

6.3.3 Population

The following criteria were used to evaluate subjects for inclusion in the study:

1. Male, age ≤ 12 years.
2. Severe hemophilia A defined as FVIII:C <1% based on documented prior testing or screening laboratory.
3. ≥ 50 ED with any FVIII concentrate (except for PUPs).
4. No current evidence of inhibitor antibody measured using the Nijmegen-modified Bethesda assay [<0.6 Bethesda units (BU)/mL] within 2-3 weeks of last FVIII administration. PTPs may not receive FVIII within 48 h prior to the collection of samples for inhibitor testing at the Screening visit.
5. No history of FVIII inhibitor formation. Documentation of negative result in medical records required. [Subjects with a maximum historical titer of 1.0 BU on no more than 1 occasion with the classical Bethesda assay but at least 3 successive negative (<0.6 BU) results thereafter are eligible.]
6. Willingness and ability of subjects and/or parents to complete training in the use of the electronic patient diary and to document injections during the study.
7. Written informed consent by parent/legal representative. Assent should be sought from subjects if appropriate.

The following criteria were used to evaluate subjects for exclusion in the study:

1. Any individual with another bleeding disorder that is different from hemophilia A (*eg*, von Willebrand (vW) disease, hemophilia B).
2. Any individual with thrombocytopenia (platelet count < 100,000/mm3).
3. Creatinine > 2x upper limit of normal or aspartate aminotransferase (AST)/alanine aminotransferase (ALT) > 5x upper limit of normal.
4. Any individual without a negative inhibitor test at screening (except for PUPs).
5. Any individual who is receiving chemotherapy, immune modulatory drugs (intravenous immunoglobulin, cyclosporine, chronic use of oral or intravenous corticosteroids), has received another investigational FVIII product within the last month, or received another experimental drug within the last 3 months.
6. Any individual who requires any pre-medication to tolerate FVIII treatment (*eg*, antihistamines)
7. Any individual who is unwilling to comply with study visits or other protocol requirements, (*e.g.*, prophylaxis treatment) or is not suitable for participation in this study for any reason, according to the Investigator's judgment.
8. Known hypersensitivity to active substance, mouse or hamster protein.
9. Previous participation in this study.

Reviewer Comment
The inclusion and exclusion criteria are acceptable.

6.3.4 Study Treatments or Agents Mandated by the Protocol

For Part A subjects, PTPs were administered 25-50 IU/kg ≥2x/week (rounded to the nearest vial size).

For any surgery, KOVALTRY was used with dosing used at the discretion of the investigator. In the event of severe or life threatening events, the subject was managed following the local standard of care, using readily available factor products.
Success is defined as (a) no detectable inhibitor on Nijmegen assay (<0.6 BU), (b) normal recovery of >66% of predicted, (c) normal half-life of ≥6 h. Failure is defined as no response (<20% decrease in the inhibitor level) within a 6-month period in the absence of any infection.

PK was collected at pre-injection, 20-30 min, 4 hours, and 24 hours after the end of injection.

6.3.5 Directions for Use

In the case of some products, particularly blood products or tissues or combination products that include devices, the protocol may specify a detailed set of instructions and/or parameters for use in the study. Document (and discuss if needed) those elements here.
No directions for use were provided in the study protocol for review.

6.3.6 Sites and Centers

There were 7 subjects enrolled in Bulgaria, 3 subjects enrolled in Canada, 2 subjects enrolled in Denmark, 7 subjects enrolled in Hungary, 1 subject enrolled in Ireland, 3 subjects enrolled in Israel, 6 subjects enrolled in Italy, 3 subjects enrolled in Lithuania, 1 subject enrolled in Latvia, 8 subjects enrolled in Poland, 7 subjects enrolled in Romania, and 10 subjects enrolled in the United States.

6.3.7 Surveillance/Monitoring

Assessments and procedures	Main study					Optional extension study	
	Visit 1 Screening	Visit 2 Baseline	Visit 3 Month 1 (± 1 week)	Visit 4 Month 2 (± 1 week)	Final visit Month 6 (≥ 50 ED)	Extension Visit every 6 months	Extension Final visit
Inclusion (date of written informed consent)	X				X		
Inclusion / exclusion criteria	X	X					
Demographic data	X						
Height, weight	X	X	X	X	X	X	X
Medical and surgical history	X						
Previous medication (medication history)	X						
Physical examination	X				X		
Adverse events	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X		
Laboratory examination [a]	X				X		
HSP-70 antibodies		X			X		
FVIII Baseline level and inhibitor (one-stage assay)	X						
FVIII level pre injection and inhibitor		X	X	X	X	X	X
Recovery (20-30 min after injection) [c]		X	X	X	X		
Pharmacokinetics (optional)	←				X [b]		→
Injection of study drug	←		continuously, in accordance with the prophylaxis regimen				→
Patient diary (EPD) documentation	←			continuously			→
Healthcare Resources Utilization Questionnaire	X	←		monthly			→
Interaction between subject/parent and investigator [d]	←		weekly		→	← monthly	→
Concomitant medication	X	←		continuously			→

a Complete blood count (CBC), chemistries.
b Blood samples at the following time points: before, 20-30 min, 4 h, and 24 h post-injection following a washout of 48 h after last dose of FVIII. Exact times need to be entered into CRF.
c. Measured at least 48 h after last dose of FVIII.
d Weekly contact during Part A, monthly during extension and 1-2 weeks after last study visit extension.

Source: CSR 13400 Table 7-1

6.3.8 Endpoints and Criteria for Study Success

The primary efficacy was the total number of bleeds or the ABR of total bleeds during prophylaxis treatment that occurs within 48 hours of the previous prophylaxis injection.

ABR under prophylaxis =
(number of bleeds) * 365.25 / (last datetime in study – 1st datetime in study) / (60*24)
where:

- 1st datetime in study is the datetime of the first prophylaxis dose (usually Visit 2)

-last datetime in study is the later of the date of Visit 6 (assume time of visit is noon) or last datetime prior to the extension period.

Secondary efficacy variables:

- ABR of total bleeds during prophylaxis treatment
- Hemostatic outcome of surgeries including blood loss, transfusion, and/or hemostatic-related surgical complications
- FVIII recovery values

Additional efficacy variables:

- ABR of joint bleeds, spontaneous bleeds, and trauma bleeds that occur within 48 hours after previous prophylaxis injection
- ABR of joint bleeds, spontaneous bleeds, and trauma bleeds
- Percentage of joint bleeds in target joint for subjects with target joint
- Number of injections (for the treatment of bleeds) per bleed
- FVIII usage for all injections and prophylaxis injections
- FVIII usage for bleeds injections
- FVIII usage for surgery injections
- Description of bleed according to type, severity, and location
- Subject's assessment of response to treatment of bleeds
- Healthcare Resources Utilization Questionnaire

6.3.9 Statistical Considerations & Statistical Analysis Plan

The analysis for the PTPS in Part A of the study was defined as the interim analysis. Summary statistics were to be provided for all efficacy variables referring to bleeds. For subjects undergoing surgery (both major and minor), study drug and blood product injections, as well as blood loss during surgery and the assessment of hemostasis during the perioperative period by the surgeon and/or the investigator were to be summarized and listed. Factor VIII concentration values and the incremental recovery values were to be summarized by time point.

6.3.10 Study Population and Disposition

Fifty eight subjects were enrolled in part A with seven screening failures.

25 PTPs were 0-<6 years and 26 were 6-12years. All the patients completed the 6 month treatment period of the study. There was one patient in the 6-12 year old age group that was excluded from per protocol analysis due to an instance of >14 days between infusions and was later found to have Type 3 von Willebrand's disease.

6.3.10.1 Populations Enrolled/Analyzed

Twelve subjects had PK evaluations performed. All of the 50 subjects treated had safety and were included in the intent to treat analysis.

6.3.10.1.1 Demographics

There were 50 males between the ages of one and eleven years of age. The following table shows the demographics and other baseline characteristics of the study population.

	Previously Treated Patients (0-<6 years) (N=25)	Previously Treated Patients (6-12 years) (N=25)	Total (N=50)
Sex			
n	25 (100.0%)	25 (100.0%)	50 (100.0%)
Male	25 (100.0%)	25 (100.0%)	50 (100.0%)
Age (years)			
n	25	25	50
Mean	3.8	8.8	6.3
SD	1.3	1.8	3.0
Median	4.0	9.0	5.5
Min	1	6	1
Max	5	11	11
Race			
n	25 (100.0%)	25 (100.0%)	50 (100.0%)
WHITE	24 (96.0%)	23 (92.0%)	47 (94.0%)
BLACK	1 (4.0%)	2 (8.0%)	3 (6.0%)
Ethnicity			
n	25 (100.0%)	25 (100.0%)	50 (100.0%)
NOT HISPANIC OR LATINO	23 (92.0%)	24 (96.0%)	47 (94.0%)
HISPANIC OR LATINO	1 (4.0%)	0	1 (2.0%)
NOT REPORTED	1 (4.0%)	1 (4.0%)	2 (4.0%)
Baseline Height (cm)			
n	25	25	50
Mean	108.3	138.1	123.2
SD	12.9	14.1	20.2
Median	114.0	138.0	121.5
Min	74	109	74
Max	126	168	168
Baseline Weight (kg)			
n	25	25	50
Mean	19.0	32.0	25.5
SD	5.3	10.4	10.5
Median	18.5	28.6	22.6
Min	11	17	11
Max	39	59	59

Source: Original from BLA 125574/0 CSR 13400 Table 14.1/1

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Hemophilia was diagnosed for all 51 patients via genetic analysis. An intron-22 inversion was present in 21.6% of these subjects. Missense mutations were detected in approximately 10% of patients. Prior to enrollment, the annualized bleeding rate and the number of joint bleeds in the younger age group was lower than in the older age group. The number of target joints was lower in the younger age group. One patient was found to have Type 3 von-Willebrand's disease (vWD) and erroneously included in the study.

6.3.10.1.3 Subject Disposition
Subjects either received on-demand (21.6%) or regular prophylaxis (78.4%) with a FVIII product prior to the study as PTPs were evaluated in Study Part A.

6.3.11 Efficacy Analyses

All of the 51 subjects were treated for efficacy analysis. Only one patient was excluded as he had a treatment interruption of >14 days which was a major protocol deviation and was found to have been misdiagnosed with HA. This patient had Type 3 vWD.

6.3.11.1 Analyses of Primary Endpoint(s)

The primary efficacy endpoint was the annualized number of total bleeds during the prophylaxis treatment that occurred within 48 hours of the previous prophylaxis injection. There were 23 subjects who experienced 53 total bleeds within 48 hours of the previous prophylaxis injection. The mean was lower in the 6 to 12 year age group than in the 0 to 6 year age group. Sixty percent of the bleeds that occurred in this time frame were trauma bleeds, 9.8 % were spontaneous bleeds and 21.6% had joint bleeds. Overall, 54.9% of patients did not experience any bleed in this time frame.

	PTPs 0 – <6 years (N = 25)	**PTPs 6 – 12 years (N = 25)**	**PTPs Total (N = 50)**
No. of total bleeds within 48 h per year			
Mean ± SD	2.23 ± 2.77	1.72 ± 3.07	1.97 ± 2.91
Median	1.88	0.00	0.00
[Q1; Q3]	[0.00; 3.97]	[0.00; 1.93]	[0.00; 2.15]
No. of total bleeds within 48 h			
Mean ± SD	1.12 ± 1.39	0.88 ± 1.56 [b]	1.00 ± 1.47
Median	1.00	0.00	0.00
[Q1; Q3]	[0.00; 2.00]	[0.00; 1.00]	[0.00; 1.00]
Sum	28	22	50
No. of subjects with ≥1 bleed within 48 h			
No [n (%)]	12 (48.0)	16 (64.0)	28 (56.0)
Yes [n (%)]	13 (52.0)	9 (36.0)	22 (44.0)

[a] "Total bleeds" include spontaneous, trauma, untreated and other reasons for injection.
[b] Underlined number changed in CSR Amendment 1 (1.59 to 1.56)
Q1 = 25% quartile; Q3 = 75% quartile.

Source: Original from BLA 125574/0; Clinical Study Report A51496, V2.0, Table 9-1

Reviewer *Comment*
It is expected that they younger age group would have an increased median ABR than the older age group. It is also expected that the the majority of bleeds woould be traumatic in origin.

The following table shows the characteristics of bleeds in the study population:

	PTPs 0 – <6 years (N = 52)	PTPs 6 – 12 years (N = 45)	PTPs Total (N = 97)
Reason for 1st injection			
n (%) [a]	44 (100.0)	37 (100.0)	81 (100.0)
Trauma bleed	36 (81.8)	23 (62.2)	59 (72.8)
Spontaneous bleed	8 (18.2)	12 (32.4)	20 (24.7)
Other	0 (0.0)	2 (5.4)	2 (2.5)
Bleeding type [b] [n (%)]			
n	52	45	97
Skin/mucosa	28 (53.8)	17 (37.8)	45 (46.4)
Joint	10 (19.2)	22 (48.9)	32 (33.0)
Number of joint bleeds (%) [c]	11 (100.0)	26 (100.0)	37 (100.0)
Ankle	5 (45.5)	7 (26.9)	12 (32.4)
Knee	2 (18.2)	5 (19.2)	7 (18.9)
Elbow	0 (0.0)	6 (23.1)	6 (16.2)
Toe	2 (18.2)	3 (11.5)	5 (13.5)
Wrist, shoulder, hand, finger, other	2 (18.2)	5 (19.2)	7 (18.9)
Muscle	5 (9.6)	4 (8.9)	9 (9.3)
Internal	1 (1.9)	1 (2.2)	2 (2.1)
Other	9 (17.3)	2 (4.4)	11 (11.3)
Bleeding severity [n (%)]			
n	52	45	97
Mild	33 (63.5)	17 (37.8)	50 (51.5)
Moderate	17 (32.7)	27 (60.0)	44 (45.4)
Severe	2 (3.8)	1 (2.2)	3 (3.1)

[a] Numbers based on "reason for 1st injection". Only bleeds treated with BAY 81-8973.
[b] Bleeds can have more than one type
[c] joint bleeds can occur in more than 1 site

Source: Original from BLA 125574/0, CSR 13400 Table 9-6

6.3.11.2 Analyses of Secondary Endpoints

Annualized number of bleeds:
The secondary efficacy endpoint included annualized number of total bleeds during prophylaxis treatment. The mean number of total bleeds per year was 3.75 ± 4.98 bleeds/year (Median: 1.90 bleeds/year). There were 97 bleeds total (81 treated bleeds: 59 trauma, 20 spontaneous, and 2 were classified as other). Of the 97 bleeds, 16 did not require an additional dose of KOVALTRY and 32 were joint bleeds. The percentage of trauma bleeds in the younger age group was higher than the older age group (81.8% vs. 62.2%, respectively).

A total of 134 injections of KOVALTRY were administered for the 97 bleeds. Sixteen bleeds resolved without an additional dose of KOVALTRY. The majority of bleeds (89.7%) were treated with ≤2 injections. The median number of days between the previous prophylaxis treatment and a bleed was 2.3 days for spontaneous bleeds and 1.9 days for traumatic bleeds. Subjects/caregivers were asked to assess the response to treatment of bleeds. This was performed in 81 of the 97 treated bleeds. The response was assessed as "good" or "excellent" in 90.1% percent of the cases. One of the bleeds was assessed as "poor".

In Vitro Recovery:
In vivo recovery (IVR) for FVIII was performed with a dose of 25-50 IU/kg. The mean recovery value for the lower age group was 1.57 and 1.72 for the higher age group at

baseline. The final mean IVR was 1.74 and 1.71 for the lower and higher age group, respectively. Complete PK assessments were only done in 12 subjects.

PK Assessments:
PK assessments were performed in a subset of 12 subjects. FVIII trough levels were measured in all subjects at each clinic visit prior to the scheduled Kovaltry injection. Levels of Kovaltry were determined with a chromogenic assay. FVIII levels of ≥2 IU/dL were maintained in 72% in the lower age group and 100% in the older age group 42-54 hours after the previous Kovaltry injection. The clearance for PTPs aged 2-6 years was 0.033dL/h/kg which was comparable to the clearance of PTPs aged 6-12years which was 0.045 dL/h.kg. The clearance was slightly increased in pediatric PTPs when compared to the clearance in adults (0.027 dL/h/kg).

Hemostatic Control During Surgery:
One subject underwent a major surgery (tooth extraction) during the study. No blood loss was reported and no transfusions were needed. The subject received 2 injections of Kovaltry on the day of surgery- 1000IU pre-surgery and 1500 IU post-surgery. Hemostasis was assessed as "good". No minor surgeries were reported.

6.3.11.3 Subpopulation Analyses

Subjects experienced more bleeds per year if they received prophylaxis ≤2x/week compared to subjects who were treated >2x/week. Subjects treated with higher doses of KOVALTRY experienced less bleeds than subjects treated with lower doses. The difference was less pronounced when the median number of bleeds/year was analyzed.

Reviewer Comment
This result did not reach any statistical significance.

6.3.11.4 Dropouts and/or Discontinuations

There was one patient in the 6-12 year old age group that was excluded from per protocol analysis due to an instance of >14 days between infusions and was later found to be misdiagnosed with HA. This patient had Type 3 vWD.

6.3.11.5 Exploratory and Post Hoc Analyses

See above.

6.3.12 Safety Analyses

All 51 patients were included in the safety analysis. The mean time on study was 182.9 days ±18 days where subjects accumulated a median of 73 exposure days (range of 37-103 EDs). The frequency of prophylaxis was 2x and 3x per week for 21 subjects in each group. Eight subjects received treatment every other day and one subject received an additional dose. The individual dosages were selected by the investigator and at their discretion. The allowed dose range was 25-50 IU/kg and was rounded to the appropriate vial size.

Reviewer Comment
There was no guidance stated in the protocol as to how the investigator was to select the doses, and was likely based on their past bleeding history.

6.3.12.1 Methods

All subjects who received at least one dose of KOVALTRY were included in the safety analysis. AEs were assessed in terms of their seriousness, severity, and relationship to study drug. Factors to be considered when associating the use of study drug and AE were: temporal sequence from drug administration, recovery on discontinuation or recurrence on reintroduction, underlying disease, concomitant medication and pharmacology of the drug.

6.3.12.2 Overview of Adverse Events

There were no deaths in the study. One subject discontinued the study drug treatment because of an AE. Nine of the sixteen were noted by the sponsor as serious AEs (5 subjects pre-treatment and 5 subjects during the treatment period with one subject overlapping both groups). Treatment-emergent AEs (AEs after the first dose and up to 3 days after the last dose) occurred in 35 subjects.

Sixteen of the 51 subjects experienced at least one AE during the screening period. The highest incidences were classified in “infections and infestations”, “gastrointestinal disorders”, and “general disorders and administration site conditions”, “respiratory, thoracic and mediastinal disorders”, “injury, poisoning and procedural complications”, and “nervous system disorders.” The subjects with AEs rated as mild, moderate, or severe. One subject experienced an AR of pruritus after start of treatment and resolved within one day which was assessed to be drug-related.

Reviewer Comment
All AEs were mild or moderate. There were 2 severe AEs which occurred, gastroenteritis and one case of anemia and constipation. The case of gastroenteritis was also noted as serious. The subject with pruritus developed this symptom 5 days after the start of treatment and resolved after a day, this is likely drug related but other factors could be attributed to the pruritus

There was one subject who developed an inhibitor development during the study in PTPs.

There was one subject with at least 1 positive antibody result for anti-HSP 70 antibody at baseline before the start of treatment and normalized by the final visit.

6.3.12.3 Deaths

Particularly for products intended for prevention of disease in generally healthy populations, reviewers may choose to evaluate and comment on each case in narrative form. Indicate your concurrence (or lack thereof) with the investigator’s assessment of causality.

For high-risk populations, summarize the natural history of the relevant diseases, focusing particularly on whether there is any discordance between the expected and observed fatality rate and on the comparison between rates in the treatment and control arms.

If death was a clinical efficacy endpoint, simply state that fact and refer to the discussion in the relevant efficacy section.

There were no deaths in this study.

6.3.12.4 Nonfatal Serious Adverse Events

There were 5 pre-treatment SAEs which included 2 central venous catheter malfunctions requiring hospitalization, 2 hemarthroses, and one altered mental status. The 5 serious adverse events during treatment included gastroenteritis, tooth abscess, nervous system disorder, hemorrhagic anemia, and bacterial infection. None of the SAEs led to discontinuation of the study drug. One of these subjects was eventually discontinued from the study during the extension period due to being misdiagnosed with Hemophilia A. This subject had Type 3 vWD.

Reviewer Comment
The subjects who experienced the pretreatment SAE are the following: two subjects with central line malfunctions; two subjects had mild hemarthrosis which required hospitalization; one subject experienced mental status changes.
The central line malfunctions were judged to be not drug related. The subjects with hemarthrosis are also judged to be not drug related.
The subjects who experienced an SAE during treatment were reviewed no to be drug related. The two cases of hemarthrosis also shows that the study drug may not have been as effective in these subjects, although they were the same subjects who reported this SAE during the pretreatment part of the study. These two subjects had previous joint damage prior to starting treatment with the study drug.

6.3.12.5 Adverse Events of Special Interest (AESI)

There was one 10 year PTP who developed a low titer inhibitor of 0.6BU/ml at ED550 during an acute pneumonia. The patient continued the treatment with the study drug without any change.

Reviewer Comment
The last inhibitor titer (as of January 15th 2016) was 1.0 BU/ml. Positive cardiolipin antibodies and lupus anticoagulant results were also noted for this subject.

6.3.12.6 Clinical Test Results

Mean and median changes from Baseline to final visit were analyzed. Overall, none of these analyses showed any relevant mean/median changes.

6.3.12.7 Dropouts and/or Discontinuations

One of the subjects discontinued study treatment due to an AE. This 4 year old subject developed a central venous catheter infection 6 months after start of treatment. Due to this, the study drug was withdrawn and additional treatment was given. This AE resolved in 3 days and was not considered drug related.

Reviewer Comment
The device related infection is not due to the study drug.

6.3.13 Study Summary and Conclusions

Fifty-eight PTPs with severe Hemophilia were included with seven screening failures. Fifty-one subjects were valid for efficacy and safety analysis. These 51 subjects were further stratified by age into two groups: 25 subjects aged 0 to<6years and 26 subjects

aged 6-12 years and evaluated for 6 months. The treatment schedule during this time frame was a frequency of every other day, 2x/week, and 3x/ week with a dose of 25-50IU/kg. Almost half of the subjects remained bleed-free during this time period. A total of 23 subjects experienced 53 bleeds with 48 hours of a previous prophylaxis injection which were mostly traumatic bleeds. The median annualized number of total bleeds during prophylaxis was 1.9 per year. The treatment was safe in this cohort of previously treated patients. None of the subjects died during the study. Only one AE was related to the study drug.
This study supports the indication for routine prophylaxis in children with Hemophilia A. It is reasonable to extrapolate the efficacy results for the on-demand data from adults to support the indication in children. As the data for control of bleeding in major surgery is limited, it is also reasonable to extrapolate from the adult study and extend this indication to children.

7. INTEGRATED OVERVIEW OF EFFICACY

The efficacy data of the Leopold I and Leopold II studies were combined. Please refer to sections 6.1 and 6.2 for details on the study designs of Leopold I and Leopold II. Please refer to the Statistical Review Memo for details.

7.1 Indications

All three indications are incorporated below.

7.1.1 Methods of Integration

The study pools for the different analyses consist of the following trials / trial parts:

The primary efficacy analysis was based on subject data from:

-Part B of Leopold I
-Prophylaxis treatment in Leopold II.

Rationale for this data pool was that only the two 6-month cross-over periods of Kovaltry prophylaxis treatment with dose determined by the CS/EP and CS/ADJ were considered for comparability. This is deemed reasonable by this reviewer.

For general efficacy analysis of prophylaxis treatment:

-Part B of Leopold I
-Extension of Leopold I
-Prophylaxis treatment in Leopold II.

Rationale for the additional inclusion of the 1-year Leopold I extension data, when only CS/EP dosing was applied, was to consider all data on bleeds and Kovaltry treatment for the assessment of general efficacy.

The main differences between the two trials were as follows:

-Prophylaxis and on-demand treatment in Leopold II versus only prophylaxis treatment in Leopold I.
-Previous treatment before enrollment was “on-demand” for 100% of Leopold II subjects versus 20% of Leopold I subjects.

-High number of previous joint bleeds resulting in high number of target joints in Leopold II subjects versus low number of previous joint bleeds and less acutely affected joints in Leopold I subjects.
-Region of conduct of trials mainly EU for Leopold I (high standard of care before study) and non-EU countries for Leopold II (low standard of care before study).
-Different assignment of dosages: 20-50 IU/kg dosed at 20, 25, 30, 35, 40, or 50 IU/kg administered 2-3 times per week at the investigator's discretion in Leopold I versus randomized low dose (20, 25, or 30 IU/kg 2x/week) or high dose (30, 35, or 40 IU/kg 3x/week) in Leopold II.
-Different duration of treatment: 2 years in Leopold I (including extension) versus 1 year in Leopold II

7.1.2 Demographics and Baseline Characteristics

Please refer to Section 6, above.

7.1.3 Subject Disposition

A total of 125 subjects were randomized to the prophylactic treatment (63 in Leopold I and 62 in Leopold II). Four of the 125 subjects (1 in Leopold I and 3 in Leopold II) never received a Kovaltry injection. Thus, the data from 121 subjects actually treated on a prophylaxis schedule (62 from Leopold I and 59 from Leopold II) were available for the pooled analysis.

7.1.4 Analysis of Primary Endpoint(s)

Pre-specified analysis
The absolute median ABRs in the PP population were 1.98 bleeds/year for both CS/EP and CS/ADJ potency assignments.

The Hodges-Lehmann estimate for the median difference between both periods of dose assignment (CS/ADJ minus CS/EP) was -0.012 bleeds/ year, with a lower limit of the 1-sided 95% CI of -1.038 bleeds/year. Since this lower limit is greater than the predefined margin of -1.5 bleeds/year, the non-inferiority of CS/EP dosing versus CS/ADJ dosing was statistically met.

7.1.5 Analysis of Secondary Endpoint(s)

As above.

7.1.6 Other Endpoints

As above.

7.1.7 Subpopulations

As above.

7.1.8 Persistence of Efficacy

As above.

7.1.9 Product-Product Interactions

N/A

7.1.10 Additional Efficacy Issues/Analyses

As requested by the FDA, the applicant provided a sensitivity analysis by excluding two subjects from the Leopold I study and nine subjects from the Sites 54001 and 54005 in the Leopold II study for the primary endpoint of the pooled analysis. Of the nine subjects from Sites 54001 and 54005 in the Leopold II study, two were randomized to the on-demand arm, and seven to the prophylaxis arms. Therefore, a total of seven subjects in prophylaxis arms and two subjects from the Leopold I study were excluded from the sensitivity analysis for pooled Leopold I and Leopold II.

The exclusion of the nine prophylaxis subjects has no substantial impact on the overall results. Non-inferiority of CS/EP-based vs CS/ADJ-based dosing in relation to prevention of bleeds during prophylaxis is unaffected.

	CS/EP 6-Month period, per-protocol set	**CS/ADJ 6-Month period, per-protocol set**	**Difference CS/ADJ - CS/EP, per-protocol set**
All subjects, N	**118**	**118**	**118**
Mean ± SD	4.4 ± 6.8	4.4 ± 6.4	-0.1±5.1
Median (Q1; Q3)	2.0 (0; 5.9)	2.0 (0; 7.3)	0.0 (-2.0; 2.0)
Median difference (2-sided 95% CI)			-0.012 (-1.23; 1.07)
Total subjects after excluding 9 subjects, N	**109**	**109**	**109**
Mean ± SD	4.6 ± 7.0	4.6 ± 6.6	-0.1 ± 5.3
Median (Q1; Q3)	2.0 (0; 6.0)	2.0 (0; 7.4)	0.0 (-2.0; 2.0)
Median difference (2-sided 95% CI) [a]			-0.004 (-1.28; 1.10)

a Hodges-Lehmann estimate

Source: Bayer's response to late-cycle meeting package, dated October 28, 2015

7.1.11 Efficacy Conclusions

The statistical reviewer verified the primary and second efficacy results for Leopold I, Leopold II, Leopold Kids studies, also the efficacy result included in the package insert based on the pooled data of the Leopold I and Leopold II studies. Based on the results of the three clinical studies, Leopold I, Leopold II, and Leopold Kids Part A, adequate statistical evidence supports the proposed indications of KOVALTRY.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

As above.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

As above.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

As above.

8.2.3 Categorization of Adverse Events

As above.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

As above.

8.4 Safety Results

8.4.1 Deaths

There were no deaths in the pooled data.

8.4.2 Nonfatal Serious Adverse Events

As above.

8.4.3 Study Dropouts/Discontinuations

As above.

8.4.4 Common Adverse Events

The most frequently reported adverse events were headache, pyrexia, and pruritus.

8.4.5 Clinical Test Results

As above.

8.4.6 Systemic Adverse Events

N/A

8.4.7 Local Reactogenicity

As above.

8.4.8 Adverse Events of Special Interest

N/A

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

N/A

8.5.2 Time Dependency for Adverse Events

N/A

8.5.3 Product-Demographic Interactions

N/A

8.5.4 Product-Disease Interactions

N/A

8.5.5 Product-Product Interactions

N/A

8.5.6 Human Carcinogenicity

N/A

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

N/A

8.5.8 Immunogenicity (Safety)

There was one 10 year old PTP who developed a low titer inhibitor of 0.6 BU/ml at ED550 during an episode of acute pneumonia. The patient continued the treatment with the study drug without any change. Testing also showed a positive lupus anticoagulant assay and therefore was not confirmed as a neutralizing antibody to FVIII.

Part B of the Leopold Kids study is an ongoing study. This study was to include to ≥25 children <6 year with ≥50 EDs of any FVIII concentrate. These subjects were also to receive prophylaxis treatment with KOVALTRY. The interim safety report submitted on April 15, 2015 showed that 4 subjects had inhibitors in the study. A detailed titer data was submitted on August 25, 2015, which showed that 14 subjects had been enrolled and treated and 3 subjects had high titer inhibitors and 3 subjects has low titer inhibitors. Those with low titers received continued treatment and the inhibitor titers resolved. Those with high titers persisted.

Reviewer Comment
In the PUPs study, the high titer inhibitor subjects did have high risk FVIII gene mutations associated with inhibitor development. The three low titer inhibitors were transient and became negative at the last measured level. The rate of inhibitors based on this data is 43% (6/14). This rate is in the upper range of expected and will be included in the PI.

8.5.9 Person-to-Person Transmission, Shedding
N/A

8.6 Safety Conclusions

KOVALTRY is well tolerated and exhibits an excellent safety profile in adults without any inhibitory antibodies to FVIII. In children, KOVALTRY is well tolerated and also has an excellent safety profile. Although one pediatric PTP out of 142 PTPs (0.7%) reported an inhibitor to FVIII, this is an accepted rate (<1.25%) of inhibitors for this safety population based on previous Advisory Committee recommendations.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

N/A

9.1.1 Human Reproduction and Pregnancy Data

N/A

9.1.2 Use During Lactation

N/A

9.1.3 Pediatric Use and PREA Considerations

KOVALTRY triggered PREA. The pediatric assessment in previously treated patients (PTP) was evaluated in the four age groups as mandated by PREA.
0 to <2 years of age: Data for PTPs below the age of 2 years are based on the Leopold Kids study. There were only 2 PTPs who had completed Part A of the Leopold Kids study. These subjects had entered the study as PTPs with ≥ 50 previous exposure days (EDs). In addition, data for 5 PTPs are provided based on the ongoing Leopold Kids Extension study for this age group. These patients had started the Leopold Kids Part B study as previously untreated patients (PUPs), completed Part B without inhibitor development, and have continued the treatment as PTPs into the Leopold Kids Extension study after they had reached at least 50 EDs during the main study.

≥2 years to <6 years of age: Data for 23 PTPs in the age range of 2 to younger than 6 years are derived from the completed Leopold Kids Part A study.
≥6 years to <12 years of age: Data for 26 PTPs from 6 to 11 years of age are derived from the completed Leopold Kids Part A study.
≥12 years to <16 years of age: Patients 12 years to less than 16 years of age were included in the Leopold I and Leopold II studies**.** A total of 13 patients were in this age group, 6 from the Leopold I Part B study and 7 from the Leopold II study.

Safety and efficacy of KOVALTRY has been demonstrated for all pediatric age groups during the development program. Individualized treatment within the ranges of dosages for prophylaxis treatment and bleeds specified in the protocols demonstrated the expected efficacy in relation to prevention of bleeds, reduction of the ABR and effective control of bleeding events.

9.1.4 Immunocompromised Patients

N/A

9.1.5 Geriatric Use

N/A

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Bioresearch Monitoring inspections of three clinical investigators were conducted in support of this BLA. Two of the clinical investigator inspections did not reveal significant problems in the study conduct. The inspection of the third clinical investigator noted significant problems that impacted the data which included 2 subjects. In addition, based on the review of the European Medicines Agency (EMA) inspection reports, and the sponsor's response to the EMA raised concerns with regard to study conduct at these sites. We requested that the sponsor submit their monitoring reports for selected clinical sites from the studies to independently assess the monitors' findings of the EMA-

inspected sites and other sites that were not inspected by the FDA. BIMO found no additional questions during our review of the monitoring reports and discussed our review with members of the BLA review team.

Due to the substantial deviations from the study protocol, and inadequacies in overall study conduct by the clinical investigators, the data for all eight subjects at Site #54005 and subject (b) (6) was excluded from final analyses.

A sensitivity analysis performed excluding these subjects did not reveal impact on the overall efficacy results.

The table below shows the evaluation of the monitoring reports submitted and the resolution involved pertaining to the study site.

Study	Site/Subject	Monitoring Report Issue	Clinical Review to Address Issue	Comments/Conclusions	Action Item/Resolution
LEO I	14001 (b) (6)	The clinical investigator (CI) requested the treatment by FVIII to be on hold for 3 to 5 days in Part A and then come back for screening and informed consent (Site 14001 monitoring report page 38)	CRF	This is not a critical violation The hold is likely due to the washout period prior to starting the study drug	None
LEO I	14001 (b) (6)	The CI changed the treatment medication from Advate to Kogenae FS between the screening day and visit-1 for this subject (Site 14001 monitoring report page 38)	CRF	Based upon the CRF, this subject was not on Advate and an erroneous entry Advate was used on subject on 1400 (b) (6)	None
LEO I	14001 (b) (6)	The monitor reports that the subject did not use the electronic patient diary (EPD) from October to December 2011	CRF	Based upon the CRF, there is no interruption of treatment Of note, there is text that supports reviewing the EPD data and an erroneous entry by the subject's mother Further records continue to capture that dosing and medication was collected by subject history	None
LEO I	65001	Six Subjects participated in Part A of the study and these are the same subjects that participated in Part B of Leopold study II at site #54005	CRF	No CRFs for site 65001	IR for CRF to be submitted; CRFs submitted and all subjects had 150 prior EDs
LEO I	65001 (b) (6)	There appears to be two SAEs that were not reported in the BLA		On page 44/62 of the ISS in Table 2-7 (2 7 4), there is documentation of both pneumonia and hematuria for this subject	None
LEO II	54001 (b) (6)	EMA inspectors noted that the subject #5400 (b) (6) was on prophylactic treatment for more than 6 months and thus did not meet eligibility criteria	Subject already excluded	Subject already excluded	None
LEO II	54001 (b) (6)	Abnormal frequency of bleeding for subject #5400 (b) (4) since July 6th requiring a FVIII antibody test for this subject the following week	CRF	As of Aug 2011, per the CRF, there was no history of Factor VIII inhibitor September 2012 was the last visit	IR to Applicant; FVIII inhibitor testing negative
LEO II	54005		Site excluded	Site excluded	None

10. CONCLUSIONS

All outstanding issues related to the review scope of this memo have been resolved.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Risk Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hemophilia A is a hereditary bleeding disorder characterized by recurrent bleeding, which if left untreated bleeds lead to chronic arthropathy, muscular atrophy and deformities. • Treatment of bleeds may delay these complications, but does not prevent it. • Primary prophylaxis with regular FVIII injections initiated at an early age is becoming the standard of care	• Hemophilia A is a hereditary, life-threatening disease • Hemophilia A can have a debilitating impact on physical and psychosocial well-being.
Clinical Benefit	• Three trials were submitted: 193 adults, adolescents, and pediatric subjects enrolled. Efficacy was demonstrated for the treatment of acute bleeds, perioperative management, and routine prophylaxis. No new safety concerns were identified. One pediatric subject developed a low-titer, inhibitor which was not associated with any clinical complications.	•The evidence for clinical benefit is compelling.
Risk	• The most substantial risks of treatment with KOVLATRY are the development of FVIII inhibitors. • No serious adverse events were found to be attributable to KOVALTRY. • No other safety signals were apparent.	• All the evidence indicates that KOVALTRY was well tolerated.
Risk Management	• The most substantial risks of treatment with KOVALTRY are the development of FVIII inhibitors. • No other safety signals were apparent.	• The package insert and the current pharmacovigilance plan, including the post-marketing studies, would be adequate to manage the risks.

11.2 Risk-Benefit Summary and Assessment

Benefits:
The benefits of KOVALTRY for the proposed indications are considered to outweigh the risks. Effective hemostasis in treatment and control of bleeding episodes and routine prophylaxis was demonstrated in adolescents and adult subjects with severe hemophilia A. Efficacy for these two indications appears comparable to that of licensed recombinant and plasma-derived Antihemophilic Factor (Human) products.

Risks:
Kogenate FS is the predecessor has shown a safety concern of inhibitor development in PUPS which has been established in the literature and in their postmarketing experience. There was one pediatric PTP that developed a FVIII inhibitor and currently an inhibitor rate of 37.5% in the ongoing PUPs study with KOVALTRY. None of the subjects in any of the trials had any thrombotic events.

The risk/benefit profile of KOVALTRY is favorable.

11.3 Discussion of Regulatory Options

N/A

11.4 Recommendations on Regulatory Actions

An approval is recommended.

11.5 Labeling Review and Recommendations

The revised package insert (PI) was reviewed, commented, and/or revised by the appropriate discipline reviewers before APLB conducted its review from a promotional and comprehension perspective. Comments and recommendations regarding the PI for this efficacy supplement were conveyed to Bayer and negotiated throughout the months of December 2015 to March 2016.

Final version of the PI submitted to the BLA in March 16, 2016 was considered acceptable.

11.6 Recommendations on Postmarketing Actions

Please see above under pharmacovigilance.