Application Type	Original BLA
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Division / Office	OBRR
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Priority Review	No
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Applicant	Bayer HealthCare
Established Name	Antihemophilic Factor (Recombinant)
(Proposed) Trade Name	Kovaltry
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	Lyophilized powder/ Intravenous
Dosing Regimen	250 IU, 500 IU, 1000 IU, 2000 IU, 3000 IU
Indication(s) and Intended Population(s)	For use in adults and children with hemophilia A for (i) on-demand treatment and control of bleeding episodes, (ii) perioperative management of bleeding, and (iii) routine prophylaxis to reduce the frequency of bleeding episodes.

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GLOSSARY

ABR	Annualized bleeding rate
AE	Adverse Event
ANOVA	Analysis of variance
BPWP	Blood products working party
BLA	Biologics License Application
BMI	Body mass index
BU	Bethesda Unit
CI	Confidence interval
CHMP	Committee for Medicinal Products for Human Use
CPMP	Clinical Investigation of Medicinal Products in the Pediatric Population
CRF	Case report form
CS/ADJ	Chromogenic substrate assay/adjusted to one-stage assay
CS/EP	Chromogenic substrate assay per European Pharmacopoeia
CSR	Clinical Study Report
DMC	Data monitoring committee
ED	Exposure Day
EMEA	European Medicines Evaluations Agency
EPD	Electronic patient diary
EU	European union
FDA	Food and Drug Administration
FVIII	Factor VIII
HSP70	Heat shock protein 70
HIV	Human immunodeficiency virus
IND	Investigation new drug
IP	Investigational product
ITT	Intent- to-treat
IU	International Unit
IV	Intravenous
pdFVIII	plasma-derived FVIII
PI	Package insert
PK	Pharmacokinetic
PP	Per-protocol
PTP	Previously Treated Patient

PUP	Previously Untreated Patient
QoL	Quality of life
rFVIII	recombinant human coagulation factor VIII
SAE	Serious adverse event
SAP	Statistical analysis plan
SID	Subject identification (number)
US	United States

1. Executive Summary

This is an original Biologics License Application (BLA) for the applicant's recombinant DNA full length Factor VIII concentrate product with the trade name of Kovaltry. Kovaltry is essentially identical to the currently marketed product Kogenate on protein concentration and the composition of the excipients. Compared to Kogenate, Kovaltry is produced with a new cell bank, which includes the gene for human heat shock protein 70 (HSP70) that improves FVIII productivity, and other improvements in the production processes.

Kovaltry is proposed for the indications of on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis treatment to reduce the frequency of bleeding episodes in adults and children with hemophilia A. This BLA contains three clinical studies, Leopold I (study 12954), Leopold II (study 14319) and Leopold Kids (study 13400), investigating efficacy and safety of Kovaltry in adults and children. Both the Leopold I and Leopold II studies are considered pivotal.

Leopold I was titled "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 (Kovaltry) in previously treated subjects with severe hemophilia A under prophylaxis therapy." The study was composed of three main parts: Part A (phase I on Pharmacokinetic [PK]), Part B (phase II/III on efficacy and safety) and Part C (major surgery) and an optional 1-year extension phase.

The primary efficacy variable in Part B was the annualized bleeding rate (ABR) of total bleeds, and the primary analysis was conducted in the 62 subjects aged 12 to 61 years in the intent-to-treat (ITT) population. The ABR (± SD) of total bleeds during the 1-year treatment period was 3.8 ± 5.2 bleeds (median: 1.0 bleed). The treatment response was assessed as "good" or "excellent" in 80.9% of the bleeding episodes. Twelve major and 26 minor surgeries were performed during the study. The hemostatic control during major and minor surgeries was good or excellent in all cases, and the blood losses did not exceed expected amounts.

There were three treatment-emergent serious adverse events (SAEs) during Part B and one SAE during Part C. None of the SAEs were rated as drug-related and all SAEs had resolved by the end of the observation period. None of the subjects died and none of the subjects discontinued study treatment due to an adverse event (AE) or SAE.

Leopold II was titled "A phase II/III, randomized, cross-over, open-label trial to demonstrate superiority of prophylaxis over on-demand therapy in previously treated subjects with severe hemophilia A treated with plasma protein-free rFVIII formulated with sucrose (Kovaltry)."

The primary objective of this study was to demonstrate the superiority of prophylaxis over on-demand treatment with Kovaltry in the prevention of bleeds as measured by the ABR in both groups. A total of 1,497 bleeds, mostly spontaneous bleeds and mild/moderate in intensity, were reported in the 80 subjects aged 14 to 59 years of the ITT population. The median ABRs were 59.96 bleeds/year in the on-demand group and 1.98 bleeds/year in the prophylaxis group. Comparison of the bleeding rates in an

analysis of variance (ANOVA) demonstrated a statistically significant difference ($p<0.0001$). The percent reduction of prophylaxis over on-demand arms in ABR using Poison regression was 91.6% (95% CI: 87.9%, 94.2%) which was statistically significantly higher than 50% reduction. The response to treatment was assessed as good or excellent in 68.2% of all bleeds during the study. One major and 20 minor surgery were performed during the study. No surgical or hemostasis-related complications were reported, and the hemostatic control was rated as good or excellent for all cases.

The two treatment-emergent SAEs were both were considered unrelated to the study treatment and both subjects recovered. None of the study subjects died and none discontinued study treatment due to an AE or SAE.

Leopold Kids was titled "A multi-center Phase III uncontrolled open-label trial to evaluate safety and efficacy of Kovaltry in children with severe hemophilia A under prophylaxis therapy". The study comprised three parts, of which only Part A was completed by the time of submission.

Part A of this study included 51 previously treated patients (PTPs) in the ITT and safety population, of whom 25 were aged between 0 and <6 years and 26 were aged between 6 and 12 years. The primary efficacy variable was ABR of total bleeds during prophylaxis treatment that occurred within 48 hours after a previous prophylaxis injection. The median ABR within 48 hours after prophylactic injection was 0.00 bleeds/year (mean, SD: 2.04±2.91). The majority (32/53) of bleeds that occurred within 48 hours after a previous prophylaxis injection were trauma related and mild or moderate in intensity. Twenty-three of 51 (45.1%) subjects reported no bleeds during the six-month treatment period. The response to treatment was assessed as "good" or "excellent" in 90.1% of the treated bleeds. One major surgery documented during Part A proceeded without complications and the hemostasis was assessed as good.

There were seven treatment-emergent SAEs in five subjects. All of them were considered unrelated to Kovaltry and all subjects recovered. None of the subjects died during the study.

As of January 15, 2016, 20 previously untreated patients (PUPs) aged 0 to 6 years have been included in Part B of this study and 16 have been treated with Kovaltry. Three PUPs developed high titer inhibitors and 4 subjects (3 PUPs and 1 PTP) developed low titer inhibitors in the Leopold Kids study.

Integrated analysis of efficacy (combining Leopold I and Leopold II)

The efficacy data of the Leopold I and Leopold II studies were combined to demonstrate the non-inferiority of the potency assignment using the Chromogenic substrate assay per European Pharmacopoeia (CS/EP) versus the Chromogenic substrate assay/adjusted to one-stage assay (CS/ADJ). This comparison was based on the ABRs during both potency periods in subjects receiving Kovaltry for prophylaxis.

The primary analysis was performed on the pooled data of 118 subjects in the per-protocol (PP) population (59 subjects each from Leopold I and Leopold II). The median ABRs were 1.98 bleeds/year in both the CS/EP and CS/ADJ periods. 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% confidence interval (CI) of -1.038 bleeds/year. This lower limit of the CI is greater than the non-inferiority margin of -1.5 bleeds/year, thus showing statistical non-inferiority of CS/EP dosing versus CS/ADJ dosing.

I verified the primary efficacy results for the Leopold I, Leopold II, Leopold Kids studies, as well as the primary efficacy result based on the pooled data of the Leopold I and Leopold II studies. No discrepancies were found. The statistical evidence supports the applicant's proposed indications for Kovaltry in BLA 125574/0.

2. Clinical and Regulatory Background

Kovaltry is a full-length rFVIII product, formulated with sucrose. It is supplied lyophilized in sterile glass vials and is reconstituted with sterile water for injection. It will be available in five vial sizes (250 International Units [IU], 500 IU, 1000 IU, 2000 IU and 3000 IU per chromogenic substrate assay).

The rFVIII protein Kovaltry is (b) (4) to the currently marketed product Kogenate FS/KOGENATE Bayer, referred to as Kogenate FS (originally approved on 25 Feb 1993 under BLA 103332); the rFVIII protein concentration and the composition of the excipients are the same as Kogenate FS. Kovaltry has an identical factor VIII (FVIII) amino acid sequence, the same molecular formula, proteolytic processing and similar post translational modification distribution (glycosylation and sulfation) as Kogenate FS. Compared to Kogenate FS, Kovaltry is produced with a new cell bank, which includes the gene for HSP70 that improves FVIII productivity, and other improvements in the production processes. In addition, all animal- and human-derived additives have been eliminated from the cell culture and purification processes and a virus filtration step has been introduced for improved non-enveloped viral clearance robustness.

Kovaltry is proposed for use in adults and children with hemophilia A (congenital Facotr VIII deficiency) for the indications of:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes

Kovaltry is not proposed for the indication of treatment of von Willebrand disease.

2.1 Disease or Health-Related Condition(s) Studied

Prevalence

Hemophilia A is considered an orphan disease with approximately 400,000 patients worldwide. It is caused by an absence or low levels of the coagulation protein FVIII. It is a lifelong X- linked disorder (the gene for FVIII is located on the X-chromosome), affecting almost exclusively males. It affects about 1 in 5000 live male births. In the United States, the mean prevalence is approximately 8 per 100,000 male individuals (Stonebraker et al. 2010).

Clinical presentation

Hemophilia A is usually diagnosed by measuring FVIII clotting activity (FVIII:C) level in the plasma of a patient. There is a direct correlation between FVIII activity levels and clinical manifestations. Hemophilia A is defined as severe if the plasma

FVIII:C level (measured as IU/dL) is <1%, moderate if it is between 1% and 5%, and mild if it is between > 5% and 40% of normal.

Hemophilia A can result in spontaneous and life-threatening bleeding events or excessive bleeding in response to trauma. Bleeds occur in muscle, organs, soft tissue and most frequently in joints, which leads to joint damage and severe disability, with major effects on the physical, psychosocial, quality of life (QoL), and financial conditions of the hemophilia patients.

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

Standard treatment for these patients is the replacement of the missing protein by infusion of exogenous FVIII concentrates, either as plasma-derived FVIII (pdFVIII) or rFVIII concentrates. Treatment regimens are either **on-demand** therapy (given when a bleed occurs) or **prophylaxis** (which consists of regular infusion of FVIII given every 2 to 3 days to prevent bleeding).

Initially, FVIII concentrates were derived directly from human plasma. However, the need for safer preparations became apparent after the transmission of viruses (hepatitis B, hepatitis C, and human immunodeficiency virus [HIV]) in the 1970s and 1980s via concentrates from plasma products without viral inactivation (Mannucci and Tuddenham 1999). The safety of pdFVIII has improved using new processes to inactivate virus, and rFVIII remains the treatment of choice for children with hemophilia A. These virus-free, recombinant products allowed for regular infusions to prevent bleeding and resultant joint damage (prophylaxis) without fear of viral transmissions, treatment at home, and thus a close-to-normal lifestyle and lifespan. The use of pdFVIII or rFVIII products varies widely across countries and regions.

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

At present, Kovaltry is neither approved for marketing nor withdrawn or suspended from marketing authorization worldwide.

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

Kovaltry has been developed under the Investigational New Drug (IND) application 14035. There were multiple pre-submission interactions between the Food and Drug Administration (FDA) and the applicant. In the pre-IND meeting of November 28, 2008, the FDA stated that the indication for routine prophylaxis should be supported by a randomized and controlled trial design evaluating the reduction in ABR between on-demand and prophylactic treatment, and preferably two different dosing regimens in the prophylactic arm. The other applicant-FDA interactions, including the pre-BLA meeting preliminary response and clarifications April – August 2014, did not have issues that relate to the statistical review of Kovaltry.

During review of the clinical data and in light of Bioresearch Monitoring inspectional findings, FDA requested Bayer to submit monitoring reports from the selected clinical sites for the Leopold I and II studies which are critical for assessment of safety and efficacy of Kovaltry in hemophilia A patients. Bayer submitted this information on September 25, 2015 in Amendment 33, which was classified as a Major Amendment, and the Action Due Date was extended to March 16, 2016.

Leopold Kids on-going Part B data was submitted on August 31, 2015 in amendment 27, on September 2, 2015 in amendment 29, and on January 22, 2016 in amendment 42.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review.

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

5.1 Review Strategy

The clinical development program of Kovaltry in hemophilia patients consists of three clinical studies, Leopold I (study 12954), Leopold II (study 14319) and Leopold Kids (study 13400), assessing efficacy and safety of Kovaltry in adults and children.

Leopold I was a phase 1, and 2/3, multicenter, open-label, non-inferiority, partially controlled (PK part), cross-over clinical trial to assess safety and efficacy (prophylaxis and perioperative) of Kovaltry in patients with severe hemophilia A.

Leopold I is completed and considered pivotal with regard to the demonstration of safety and efficacy in accordance with the European *'Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products'*.

Leopold II was a phase 2/3, randomized, cross-over trial to demonstrate the superiority of prophylaxis over on-demand therapy by a clinically significant decrease in the bleeding rate during 12 months of treatment with Kovaltry.

Leopold II is completed and considered pivotal with regard to the routine prophylaxis indication in adults in the United States (US) and supportive with regard to European requirements.

Leopold Kids is a phase 3, multicenter, open-label, uncontrolled study to demonstrate the safety and efficacy of the treatment with Kovaltry for prophylaxis, breakthrough bleeds, and surgery in children with severe hemophilia A. The study comprised three parts, however only data from the completed Part A and the ongoing part B (as of January 15, 2016) has been submitted to the file.

Due to the importance of these three studies and the study results included in the package insert (PI), they will be reviewed individually in detail in section 6.

Also, in an addendum to the Leopold I report, the efficacy data of the Leopold I and Leopold II studies were combined to demonstrate the non-inferiority of the CS/EP potency assignment in comparison to the CS/ADJ potency assignment based on the comparison of ABRs during both potency periods in subjects receiving Kovaltry for prophylaxis. Therefore, the pooled efficacy analysis results presented in the PI will be reviewed in section 7.1. The perioperative results for Leopold I and II are also reviewed in section 7.1.

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

- Original submission under BLA 125574/0
  - Module 1.14: Labeling
  - Module 2.5: Clinical Overview

- Module 2.6: Clinical Summary
- Module 5.3.5.2: Clinical Study Reports (CSRs) for Leopold I (study 12954), Leopold II (study 14319), Leopold Kids (study 13400), Statistical Analysis Plans (SAPs) and tabulation data

  Leopold I (study 12954)
  - The CSR (1363 pages), dated September 1, 2014, with 155-page main text.
  - The Protocol (331 pages), Version 10.0, dated April 1, 2011.
  - The SAP (26 pages), Version 2.3, dated August 1, 2012.

  Leopold I Extension (study 12954 Addendum1)
  - The CSR (583 pages), dated August 30, 2013, with 69-page main text.
  - The Protocol (331 pages), Version 10.0, dated April 1, 2011.
  - The SAP (17 pages), Version 1.0, dated April 29, 2013.

  Leopold I and Leopold II Integrated Analysis (study 12954 Addendum2)
  - The CSR (440 pages), dated December 17, 2014, with 51-page main text.
  - The Protocol (331 pages), Version 10.0, dated April 1, 2011.
  - The SAP (46 pages), Version 1.1, dated October 13, 2013.

  Leopold II (study 14319)
  - The CSR (938 pages), dated September 1, 2014, with 97-page main text.
  - The Protocol (203 pages), Version 4.1, dated March 15, 2011.
  - The SAP (24 pages), Version 1.4, dated February 13, 2013.

  Leopold Kids (study 13400)
  - The CSR (384 pages), dated September 1, 2014, with 73-page main text.
  - The Protocol (210 pages), Version 3.0, dated August 30, 2012.
  - The SAP (17 pages), Version 2.1, dated December 19, 2012.

- Amendments under BLA 125574/0
  - Amendment 125574/0.15
    - Module 5.3.5.2 Additional information to Leopold Kids: Leopold Kids (13400) PUP Inhibitor Listing (Cut-Off Date 31Dec2014)
    - Module 5.3.5.3 Integrated Analysis
  - Amendment 125574/0/20
    - Response to Information Request
  - Amendment 125574/0/23
    - Updates of Package Insert
  - Amendment 125574/0.27
    - Module 5.3.5.2 Additional Information to Leopold Kids: Leopold Kids (13400) Inhibitor Cases (Cut-Off Date 25Aug2015)
  - Amendment 125574/0.29
    - Response to Information Request
  - Amendment 125574/0.32
    - Response to Information Request
  - Amendment 125574/0.36
    - Slide deck for late-cycle meeting
  - Amendment 125574/0.37

- Response to late-cycle meeting package (Clinical)
- Module 5.3.5.2 Leopold I and Leopold II sensitivity analysis for integrated primary efficacy excluding sites 14006 and 54005 and subject (b) (6)
- Module 5.3.5.2 Leopold Kids Confidence Intervals for Inhibitor Cases (all and high titer) (Cut-Off Date 25Aug2015)
- Module 5.3.5.2 Leopold II sensitivity analysis per Poisson primary and secondary comparison of ABR; Leopold II subgroup analysis by race ABR

- Amendment 125574/0.40
  - Updates of Package Insert
- Amendment 125574/0.41
  - Updates of Package Insert
- Amendment 125574/0.42
  - Response to Information Request (Clinical)
  - Module 5.3.5.2 Leopold Kids (13400) Updated Inhibitor Data (Cut-Off Date 15Jan2016)
- Amendment 125574/0.43
  - Updates of Package Insert

5.3 Table of Studies/Clinical Trials

The clinical development program of Kovaltry consists of three studies. An overview of these studies is provided in Table 1.

Table 1. Clinical development program: overview of clinical studies to evaluate efficacy and safety

Study name, Phase	Design	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)**					
PartA Phase 1	Randomized, non-inferiority, single-dose, open-label, intra-individual, cross-over, controlled, PK	To demonstrate the PK non-inferiority of Kovaltry as compared to Kogenate FS using bioequivalence criteria	50 IU/kg of Kovaltry or Kogenate FS; CS/EP potency (dose) assignment Two single IV injections, and at least a 3-day washout period between treatments	PTPs, male, 12-65 years of age	PK analysis[a] (Part A): 26 PK analysis[a] (Parts A+B): 19
PartB Phase 2/3	Randomized, open-label, intra-individual, cross-over for 2 different potency assignments	To demonstrate the efficacy and safety of Kovaltry for the treatment of bleeds and prophylaxis Repeat PK	20-50 IU/kg of Kovaltry, CS/EP and CS/ADJ potency assignment[b] 2 – 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
PartC Phase 2/3	Open-label	To assess the hemostatic outcome of treatment with Kovaltry during major surgery	Treatment only during hospital stay from pre-operation to 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	Kovaltry potency by CS/EP only. Treatment as in Part B, with one-time dose adjustment permitted at start of Extension. One more year	Subjects who completed Part B and wished to continue	Entered the Extension: 55

Study name, Phase	Design	Study objectives	Dose and regimen Treatment duration	Study population	Number of patients by treatment group (Intent-to-treat set)[a]
'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
'Leopold Kids' **Report no. A51496 (protocol no. 13400)**					
PartA Phase 3	Multicenter, uncontrolled, open-label	To demonstrate the safety and efficacy of treatment with Kovaltry for prophylaxis and breakthrough bleeds in children, optional PK in any part of the study	25 – 50 IU/kg prophylaxis at least 2x/week, treatment of breakthrough bleeds and peri-operative management of bleeding approx. 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
PartB 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

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: Leopold I (Protocol 12954)

Leopold I study is titled "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 (Kovaltry) in previously treated subjects with severe hemophilia A under prophylaxis therapy." The study was composed of three main parts: Part A (phase I on Pharmacokinetic [PK]), Part B (phase II/III on efficacy and safety) and Part C (major surgery) and an optional 1-year extension phase.

6.1.1 Objectives (Primary, Secondary, etc)

Part A (Phase I)

Primary objective:

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

Secondary objective:

- To evaluate the *in vivo* recovery of FVIII plasma level 15 minutes post single injection of Kovaltry

Part B (Phase II-III)

Primary objective:

- To demonstrate the efficacy and safety of Kovaltry for the treatment of bleeds and prophylaxis.

Secondary objectives:

- To compare bleeding frequency of prophylactic treatment with Kovaltry dose determined by CS/EP versus dose determined by 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 HSP70 and/or hamster proteins during prophylactic treatment with Kovaltry.
- To evaluate surgical outcomes during treatment with Kovaltry.
- To assess QoL and pharmaco-economic parameters during prophylactic treatment with Kovaltry.
- To assess the safety and tolerability profile of Kovaltry by assessing clinical chemistry, hematological parameters, and adverse event (AE) presentation.

Part C (major surgery)

- To evaluate surgical outcomes during treatment with Kovaltry.

Extension part

- To assess the long term safety and efficacy treatment profile of Kovaltry (up to 2 years of treatment).

6.1.2 Design Overview

Part A A phase-I, randomized, non-inferiority, single-dose, open-label, cross-over pharmacokinetic trial with Kovaltry

Part A was to demonstrate PK non-inferiority of 50 IU/kg of Kovaltry to Kogenate FS using bioequivalence criteria in up to 30 previously treated subjects using a single-dose, intra-individual, cross-over trial design. The potency for both products was determined by the CS/EP.

Only subjects who completed Part A were permitted to continue (be randomized) into Part B prior to the gating decision. These subjects were the only ones that overlapped between Parts A and B.

The results from this part of the study are not covered in this review and are deferred to the clinical pharmacologist.

Part B A phase II/III, randomized, open-label, cross-over trial to assess the safety, tolerability and efficacy of prophylaxis therapy in subjects with severe hemophilia A treated with Kovaltry

Part B was to assess the safety, tolerability and efficacy of prophylaxis treatment using 20-50 IU/kg of Kovaltry administered 2-3 x/week to 60 subjects using an intra-individual (investigator assigned), cross-over trial design. Once a subject had been assigned a certain prophylaxis dose, the assignment was to be maintained for the duration of the trial.

Sixty subjects were to be randomized with ratio 1:1 to two treatment arms. Subjects in both treatment arms were to receive open-label prophylactic administration of Kovaltry, but the doses for the two periods in each treatment arm were to be calculated using potency assignments determined by either CS/EP or CS/ADJ according to randomization (CS/EP → CS/ADJ, or CS/ADJ → CS/EP).

Subjects enrolled in each of the two arms were to undergo prophylaxis treatment for 6 months according to their initial potency assignment. After a minimum of a 2-3-day washout period, subjects were to cross over to the alternate potency assignment for the second 6-month treatment period. The total study duration per subject was approximately 12 months.

The dosing for breakthrough bleeds was to be dependent upon the bleeding location and severity and had to be consistent with acceptable standards of care. All breakthrough bleeds were to be treated with Kovaltry.

In vivo recovery was to be assessed twice during each period, at the start and at 3 months or at the end of each 6-month potency assignment period.

Subjects requiring any surgeries during Part B of the study were to be treated with Kovaltry and were included in the assessments of efficacy and safety.

Part C A Major Surgery Arm for assessment of hemostatic outcome of treatment with Kovaltry during major surgery in additional subjects who did not participate in Part B

Kovaltry was not supplied for use in the surgical setting until at least 20 bleeding events had been assessed, to ensure the hemostatic activity of Kovaltry. All sites were informed by the applicant when surgical treatment using Kovaltry was allowed to commence. Other FVIII products could be used for surgery, if needed, before the approval by the Data Monitoring Committee (DMC) for the use of Kovaltry in a surgical setting.

These subjects were to receive treatment with CS/EP potency assignment only during their hospital stay from pre-operation to their discharge (not exceeding a total of 3 weeks). These subjects were to be considered to have completed the study at the time of their discharge or after maximum treatment duration of 3 weeks. For subjects participating in Part C only, the same data were to be collected during study participation as for subjects participating in Part B and undergoing a major surgery.

Extension part

The extension phase of the study was to include subjects who completed the one year study period in Part B to collect additional safety and efficacy data. This extension phase was planned for a period of up to 1 year.

Pre-medications were not to be administered for injections of Kovaltry. The planned total duration of treatment overall for the subjects in Part B and the extension period was up to 24 months.

6.1.3 Population

Subject eligibility criteria:

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 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) 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 rFVIII or pdFVIII only. 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 two 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 two 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 one occasion but with at least three 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.

6.1.4 Study Treatments

Part B

Prophylaxis treatment

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 intravenous (IV) injection over 1 – 15 minutes.

Treatment of breakthrough bleeds

All breakthrough bleeds during prophylaxis treatment were to be treated with Kovaltry according to the bleeding location and severity and to current standards of care.

Treatment during surgery

During surgery, dosing was to follow the same standard of practice as recommended in the prescribing information for Kogenate FS. Subjects were to continue prophylaxis therapy before and after recovery from surgery.

Extension part

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 assignment determined by CS/EP)
Route of administration:	Manual IV injection over 1 – 15 minutes.

6.1.6 Sites and Centers

The study was conducted at 26 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 US (5).

6.1.8 Endpoints and Criteria for Study Success

Part B

Primary efficacy variable was the ABR for total bleeds (i.e., spontaneous and trauma bleeds, untreated bleeds and bleeds of missing reason) in each 6-month potency assignment period. Success was achieved if the ABR decreased at least 50% compared to the previous year's ABR.

Other efficacy variables include:

- 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"(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.)
- 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 (Excellent: perioperative blood loss similar to the non-hemophilic patient; Good: perioperative bleeding slightly but not clinically significantly increased over expectations for the non-hemophilic patient. Treatment similar to non-hemophilic patient).
- 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 as assessed by the surgeon (including blood loss, transfusion, and/or hemostasis-related surgical complications).

Extension part
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.

6.1.9 Statistical Considerations & Statistical Analysis Plan

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.

Subgroup analyses
Major subgroups planned for some efficacy and safety analyses as well as for Baseline and extent of exposure included age (<18 years or ≥18 years) and treatment regimen (2x or 3x/week prophylaxis). Further possible subgroup analyses planned for the primary efficacy variable included: age (years < 18, 18- < 30, ≥ 30), race (White, non-White), dose (high: 35-50 IU/kg or low: 20-30 IU/kg), and region (Europe, Israel, United States, or South Africa).

Sample size determination
The sample size of 60 subjects is based on regulatory requirements (European Medicines Evaluations Agency [EMEA]/ Committee for Medicinal Products for Human Use [CHMP]/ Blood Products Working Party [BPWP]/144533/2009: Recombinant and Human FVIII derived products).

Handling of missing data
If dates for bleeds and infusions are both missing then these bleeds/infusions cannot be counted. Each subject's period start and stop date were to be needed to compute the annualized bleeding rate. If the bleed date is missing, but the infusion date is

available, infusion date was to be used. Imputation rules were specified in "Analysis Datasets" document.

Statistical methodology
The number of data available and missing data, mean, standard deviation, median, minimum and maximum values and other summary statistics were to be calculated for continuous data. Frequency tables were to be generated for categorical data.

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

Bleeding rate will be annualized as follows:

ABR = (# of bleeds)*365.25/((last datetime - first datetime)/(60*60*24))

FVIII concentrations and recovery values (one-stage and chromogenic assays) were to be summarized and listed for each time point.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A summary of the different analysis sets is given in Table 2. For Part B, the ITT population consisted of 62 subjects.

Table 2. Analysis sets of the different parts of the study (all treated subjects)

	Safety population	ITT population	PP population	PK analysis population
Part A (PK part)				
BAY 81-8973	28	-	-	26
Kogenate FS	28	-	-	26
Completed Part A and Part B	21	-	-	19
Part B (prophylaxis part)				
CS/EP → CS/ADJ	30	30	29	-
CS/ADJ → CS/EP	32	32	30	-
Combined	62	62	59	-
Part C (major surgery part)				
Treated in Part C	5	5	-	-
Part B subjects with major surgeries	-[a]	3	-	-
Combined major surgeries	-	8	-	-

[a] Subjects with major surgeries during the extension period were included in the safety population of Part B.

Source: Original from BLA 125574/0; Clinical Study Report A62366, V3.0, Table 8-1

Extension part
All of the 55 subjects who continued prophylaxis treatment during the extension part were included in the efficacy and safety analysis.

6.1.10.1.1 Demographics

Part B
Sixty-two male subjects aged between 12 and 61 years (median: 30.0 years) received treatment with Kovaltry in Part B. A total of 10 subjects, 5 in each treatment period, were children aged between 12 and 17 years.

The majority of the subjects (55/62, 88.7%) were of White race, 4 were Black, 2 were Hispanic and 1 was of mixed race ("uncodable"). No Asian subjects participated in

Part B. The two treatment periods were well balanced with regard to demographics and other Baseline characteristics. A summary of these data is shown in Table 3.

Table 3. Demographic and other baseline characteristics of subjects in Part B (all safety Part B subjects)

	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: Original from BLA 125574/0; Clinical Study Report A62366, V3.0, Table 8-4

Part C

All of the eight subjects in the Major Surgery Arm (including the three subjects who underwent major surgeries during the Part B extension) were adults of White race. Their mean age was 36.4 years (age range: 28 – 41 year).

6.1.10.1.2 Disease Characterization of the Enrolled Population

All 62 subjects participating in Part B had a documented FVIII:C <1% and no history of inhibitor. The most recent treatment regimen for hemophilia prior to enrolment was prophylaxis in 80.6% of subjects, and on-demand treatment in 19.4% of subjects.

At Baseline, 44 of the 62 subjects (71.0%) had at least 1 target joint for bleeds. The median number of target joints in the Part B population was 1 (maximum: 5). There was a high variability among subjects regarding the number of bleeds in the previous 12 months before enrollment. Overall, the median number of bleeds in the previous 12 months was 5.5 and ranged between 0 and 55 bleeds, mostly joint bleeds.

An overview of these data is shown in Table 4.

Table 4. Disease characteristics of subjects in Part B (all safety Part B subjects)

	CS/EP → CS/ADJ (N = 30)	CS/ADJ → CS/EP (N = 32)	Total (N = 62)
Most recent treatment [a] [n (%)]			
on-demand	4 (13.3)	8 (25.0)	12 (19.4)
prophylaxis	26 (86.7)	24 (75.0)	50 (80.6)
Target joint for bleeds [n (%)]			
no	10 (33.3)	8 (25.0)	18 (29.0)
yes	20 (66.7)	24 (75.0)	44 (71.0)
Number of target joints			
n	30	32	62
Mean ± SD	1.2 ± 1.1	1.6 ± 1.4	1.4 ± 1.3
Median	1.0	1.0	1.0
[Min; Max]	[0; 4]	[0; 5]	[0; 5]
No. of bleeds in the last 12 months			
n	30	32	62
Mean ± SD	12.3 ± 13.8	10.8 ± 16.4	11.5 ± 15.1
Median	8.5	4.0	5.5
[Min; Max]	[0; 55]	[0; 53]	[0; 55]
No. of bleeds in the last 12 months (prior treatment: prophylaxis)			
n	26	24	50
Mean ± SD	8.5 ± 9.3	5.1 ± 7.5	6.9 ± 8.6
Median	8.0	4.0	4.0
[Min; Max]	[0; 40]	[0; 37]	[0; 40]
No. of bleeds in the last 12 months (prior treatment: on-demand)			
n	4	8	12
Mean ± SD	36.8 ± 14.3	28.0 ± 23.7	30.9 ± 20.8
Median	36.0	28.5	36.0
[Min; Max]	[20; 55]	[0; 53]	[0; 55]
No. of joint bleeds in the last 12 months			
n	30	32	62
Mean ± SD	10.5 ± 13.8	5.6 ± 9.3	8.0 ± 11.9
Median	6.0	3.0	3.5
[Min; Max]	[0; 55]	[0; 47]	[0; 55]

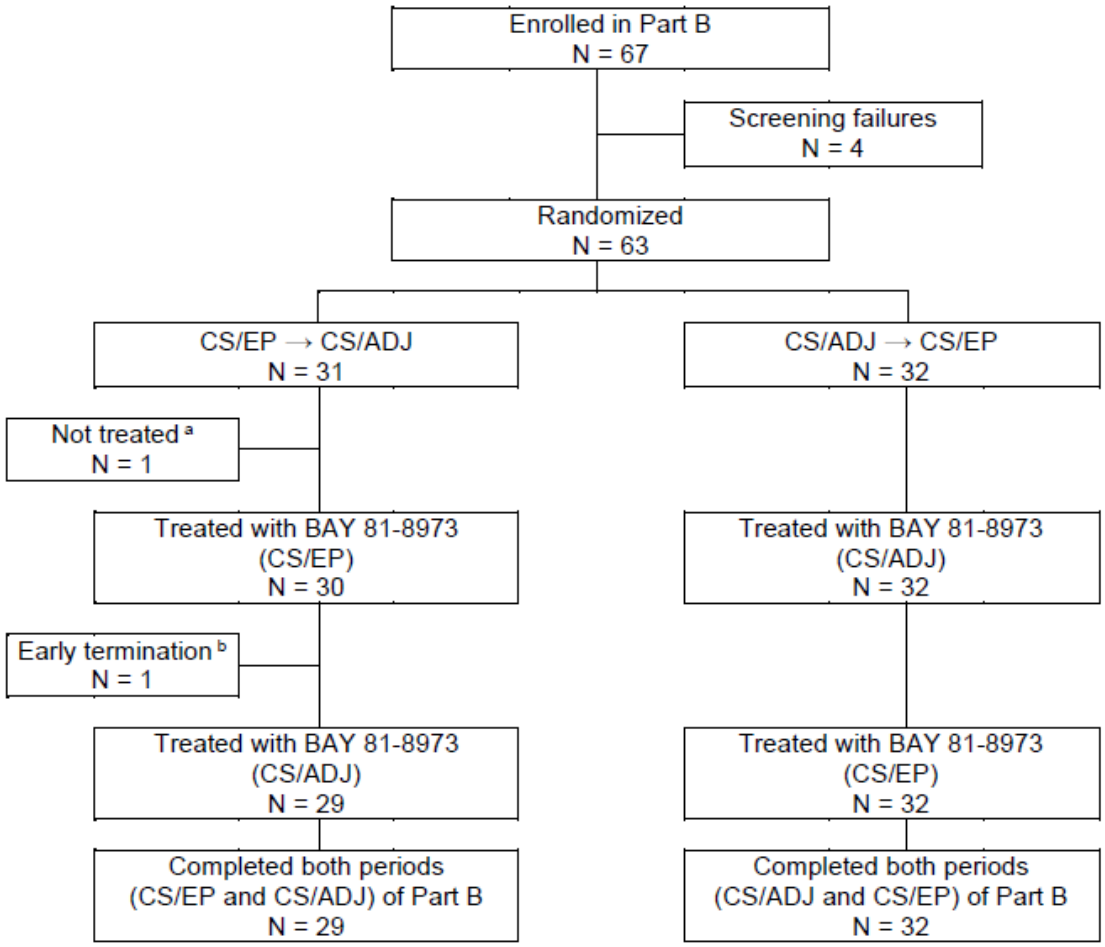
[a] Refers to most recent treatment prior to enrollment, not to long-term treatment.
Source: Adapted from BLA 125574/0; Clinical Study Report A62366, V3.0, Table 8-7

6.1.10.1.3 Subject Disposition

Part B

Figure 1 shows the subject disposition of all subjects enrolled in Part B.

Figure 1. Subject disposition in Part B (all Part B subjects)



[a] Reason for not being treated: Subject withdrew consent.
[b] Reason for early termination: Protocol violation.

Source: Original from BLA 125574/0; Clinical Study Report A62366, V3.0, Figure 8-2

Extension part

Fifty-five of the 61 subjects who had completed Part B continued prophylaxis treatment in the extension period, and 43 of these subjects (78.2%) completed the 1-year extension period.

Of the 12 subjects, who discontinued before completion, 8 started another study, and 1 subject each discontinued the extension period because of an adverse event, withdrawal of consent, investigator's decision (not protocol-driven, but due to a planned orthopedic surgery), and non-compliance with study medication.

Twelve major surgeries had been performed with Kovaltry treatment up to the end of the extension period. Five of these subjects participated in the extension period and seven major surgeries were performed in seven subjects in Part C. One further subject was enrolled in Part C, but actually did not undergo surgery (screening failure).

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Part B

During the whole course of treatment (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). Of these, 153 bleeds (64.8%) were spontaneous bleeds, 79 bleeds (33.5%) were trauma bleeds, and 4 (1.7%) were untreated bleeds, *i.e.*, bleeds that did not require additional injections besides the scheduled regular prophylaxis injections, which were due.

The mean (± SD) of the individual ABRs during the study was 3.79 ± 5.21 bleeds/year with an interquartile range between 0.00 and 5.09 bleeds/year (median: 1.03 bleeds/year). The mean (± SD) of the individual ABRs in the last 12 month before the study was 11.5 ± 15.1 bleeds/year (median: 5.5 bleeds/year) (see Table 4). Both the mean and median ABR decreased more than 50% compared to the previous year's ABR. Mean ABRs for the two potency assignments (CS/EP and CS/ADJ) were similar.

Considering only the data of subjects with prophylaxis as most recent treatment (n=50), the mean (± SD) of the individual ABRs during the study was 3.67 ± 5.23 bleeds/year (median: 1.03 bleeds/year), much lower than in the year before the study (mean ± SD: 6.9 ± 8.6 bleeds/ year; median: 4.0 bleeds/year) (see Table 4).

Table 5 gives an overview on the results of the analysis of the primary efficacy variable in the ITT population.

Table 5. Number of total bleeds [a] (Part B ITT population)

	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
n=number of subjects (excludes missing data)
sum=number of bleeds
Source: Original from BLA 125574/0; Clinical Study Report A62366, V3.0, Table 9-1

Supportive analysis

The FDA Bioresearch Monitoring (BIMO) inspection of US site 14006 identified failure to conduct required testing for inhibitors and under-reporting of bleeding episodes and adverse events for the two subjects. FDA requested the applicant to perform sensitivity analysis for the primary efficacy endpoint by excluding the two

subjects from this site in the late cycle meeting package sent to the applicant on September 25, 2015.

Table 6 showed the summary statistics for the ABR with and without the two subjects provided by the applicant. The mean ABRs are comparable between two analyses; the median ABR increased to 1.5 bleeds/year from 1.0 bleeds/year after excluding the two subjects.

Table 6. Number of total bleeds (Part B ITT population, with and without 2 subjects from site 14006)

ABR	CS/EP 6-Month Period	CS/ADJ 6-Month Period	Combined
All subjects (N)	**62**	**61**	**62**
Mean	3.5	4.1	3.8
Median (Q1; Q3)	1.9 (0; 4.4)	1.9 (0; 7.3)	1.0 (0; 5.1)
Excluding 2 subjects (N)	**60**	**59**	**60**
Mean	3.5	4.3	3.9
Median (Q1;Q3)	1.9 (0; 4.5)	2.0 (0; 7.4)	1.5 (0; 5.5)

Source: Bayer late-cycle meeting slides submitted on Oct 8, 2015

Extension part

During the study extension, 46 of the 55 subjects experienced a total of 154 bleeds. Of these, 79 (51.3%) were spontaneous bleeds, 70 (45.5%) were trauma bleeds, 4 (5.2%) were untreated bleeds, and 1 were “other reason” (e.g., additional prophylaxis injections for expected bleeds due to increased physical activity).

The mean (± SD) of the individual ABRs for the 55 subjects was 3.71 ± 4.98 bleeds/year (median: 1.97 bleeds/year). This shows a trend towards a decrease in the ABR during the latter part of the study as the Part B ABR was 4.21 ± 5.42bleeds/year, paralleled by an increase in the number of bleed-free subjects in the second year (23.6% for Part B versus 32.7% for the extension). However, the median ABRs were almost identical in both years (2.01 and 1.97 bleeds/year, respectively).

Table 7 gives an overview of the Part B (only the subjects who enrolled in the extension), extension, and combined results of the analysis of the primary efficacy variable in the ITT population.

Table 7. Number of all bleeds[a] (Extension ITT population)

	Part B / Year 1 (N = 55)	Extension / Year 2 (N = 55)	Combined / Year 1+2 (N = 55)
Time in study [days]			
n	55	55	55
Mean ± SD	364.3 ± 5.8	329.9 ± 88.3	694.2 ± 87.0
Median	364.0	365.0	729.6
[Min; Max]	[348; 376]	[22; 377]	[386; 749]
No. of all bleeds			
n	55	55	55
Mean ± SD	4.2 ± 5.4	2.8 ± 3.7	7.0 ± 8.7
Median	2.0	1.0	4.0
[Q1; Q3]	[1; 6]	[0; 5]	[1; 11]
Sum	232	154	386
No. of all bleeds per year			
n	55	55	55
Mean ± SD	4.21 ± 5.42	3.71 ± 4.98	3.76 ± 4.61
Median	2.01	1.97	1.99
[Q1; Q3]	[0.98; 6.09]	[0.00; 5.21]	[0.50; 5.48]

[a] "All bleeds" include spontaneous, trauma, untreated bleeds, bleeds with missing reason and "other reason" for injection.
Q1 = first quartile, Q3 = third quartile
n=number of subjects (excludes missing data)
sum=number of bleeds
Source: Original from BLA 125574/0; Clinical Study Report PH37225, V1.0, Table 9-1

6.1.11.2 Analyses of Secondary Endpoints

Annualized numbers of all, joint, and spontaneous bleeds in each 6-month potency assignment period

Part B

All bleeds

The total number of all bleeds (includes "total bleeds" and injections for which the reason was "other") was 241; 51.8% of bleeds were classified as mild, 38.2% as moderate and 10.8% of the bleeds were severe. Sixteen of the 62 subjects (25.8%) did not experience any bleeds during the 1-year treatment period. The mean (± SD) ABR across both periods was 3.87 ± 5.21 bleeds/year with an interquartile range between 0.00 and 5.09 bleeds/year (median: 1.92 bleeds/year).

Spontaneous bleeds

The total number of spontaneous bleeds reported was 153 (64 during the CS/EP period and 89 during the CS/ADJ period). The mean (± SD) ABR across both periods was 2.46 ± 3.50 with an interquartile range between 0.00 and 3.94 bleeds/year (median: 1.01).

Joint bleeds

A total of 191 joint bleeds occurred (87 during the CS/EP period and 104 during the CS/ADJ period). The mean (± SD) ABR was 3.07 ± 4.66 with an interquartile range between 0.00 and 3.00 (median: 1.04). The mean ABRs were within the same range in the CS/EP period as in the CS/ADJ period but with a higher median in the CS/ADJ period (1.78 bleeds/year vs 0 bleeds/year).

For a summary of these data, see Table 8.

Table 8. Summary of bleeds (Part B ITT population)

	CS/EP (N = 62)	CS/ADJ (N = 61)	Combined (N = 62)
No. of all bleeds [a]			
n	62	61	62
Mean ± SD	1.8 ± 2.6	2.1 ± 3.2	3.9 ± 5.2
Median	1.0	1.0	2.0
[Q1; Q3]	[0.0; 2.0]	[0.0; 4.0]	[0.0; 5.0]
Sum	111	130	241
No. of spontaneous bleeds			
n	62	61	62
Mean ± SD	1.0 ± 1.8	1.5 ± 2.4	2.5 ± 3.5
Median	0.0	0.0	1.0
[Q1; Q3]	[0.0; 2.0]	[0.0; 2.0]	[0.0; 4.0]
Sum	64	89	153
No. of spontaneous bleeds per year			
n	62	61	62
Mean ± SD	2.04 ± 3.62	2.85 ± 4.61	2.46 ± 3.50
Median	0.00	0.00	1.01
[Q1; Q3]	[0.00; 3.04]	[0.00; 3.93]	[0.00; 3.94]
No. of joint bleeds			
n	62	61	62
Mean ± SD	1.4 ± 2.5	1.7 ± 2.8	3.1 ± 4.7
Median	0.0	1.0	1.0
[Q1; Q3]	[0.0; 2.0]	[0.0; 2.0]	[0.0; 3.0]
Sum	87	104	191
No. of joint bleeds per year			
n	62	61	62
Mean ± SD	2.79 ± 4.96	3.33 ± 5.41	3.07 ± 4.66
Median	0.00	1.78	1.04
[Q1; Q3]	[0.00; 3.93]	[0.00; 4.01]	[0.00; 3.00]

[a] "All bleeds" include "total bleeds" and injections for which the reason for injection was "other".
n=number of subjects (excludes missing data)
sum=number of bleeds
Source: Adapted from BLA 125574/0; Clinical Study Report A62366, V3.0, Table 9-4

Extension part

All bleeds

The number of total bleeds reported during the extension was 153. Eighteen of the 55 subjects (32.7%) did not experience any bleeds during the extension period. The mean (± SD) ABR was 3.69 ± 4.94 bleeds/year (median: 1.97 bleeds/year). The ABR was slightly higher in the first than in the second year of treatment (4.16 ± 5.42 bleeds/year during Part B). During the extension, 48.6% of the bleeds were classified as mild, 39.0% as moderate and 12.5% of the bleeds were severe.

Spontaneous bleeds

The total number of spontaneous bleeds reported during the extension was 79, with a mean (± SD) ABR of 1.79 ± 3.01 spontaneous bleeds/year (median: 0.98).

Joint bleeds

A total of 120 joint bleeds were reported during the extension. The mean (± SD) ABR was 2.68 ± 3.87 with an interquartile range between 0.00 and 3.94 (median: 1.02).

For a summary of these data (Part B [only the subjects who enrolled in the extension], extension, and combined), see Table 9.

Table 9. Summary of bleeds (Extension ITT population)

	Part B / Year 1 (N = 55)	Extension / Year 2 (N = 55)	Combined / Year 1+2 (N = 55)
No. of total bleeds [a]			
n	55	55	55
Mean ± SD	4.2 ± 5.4	2.8 ± 3.6	6.9 ± 8.6
Median	2.0	1.0	4.0
[Q1; Q3]	[0.0; 6.0]	[0.0; 5.0]	[1.0; 11.0]
Sum	229	153	382
No. of total bleeds per year [a]			
n	55	55	55
Mean ± SD	4.16 ± 5.42	3.69 ± 4.94	3.72 ± 4.58
Median	1.98	1.97	1.99
[Q1; Q3]	[0.00; 6.09]	[0.00; 5.21]	[0.50; 5.48]
No. of spontaneous bleeds			
n	55	55	55
Mean ± SD	2.7 ± 3.7	1.4 ± 2.1	4.1 ± 5.4
Median	1.0	1.0	2.0
[Q1; Q3]	[0; 4]	[0; 2]	[1; 5]
Sum	148	79	227
No. of spontaneous bleeds per year			
n	55	55	55
Mean ± SD	2.68 ± 3.64	1.79 ± 3.01	2.25 ± 3.06
Median	1.02	0.98	1.00
[Q1; Q3]	[0.00; 3.99]	[0.00; 1.99]	[0.49; 3.26]
No. of joint bleeds			
n	55	55	55
Mean ± SD	3.3 ± 4.9	2.2 ± 3.2	5.5 ± 7.6
Median	1.0	1.0	2.0
[Q1; Q3]	[0; 4]	[0; 3]	[0; 8]
Sum	184	120	304
No. of joint bleeds per year			
n	55	55	55
Mean ± SD	3.34 ± 4.87	2.68 ± 3.87	2.95 ± 4.05
Median	1.05	1.02	1.49
[Q1; Q3]	[0.00; 4.06]	[0.00; 3.94]	[0.50; 3.97]

[a] "Total bleeds" include spontaneous and trauma bleeds, untreated bleeds and bleeds with missing reason.

[c] Only subjects with ≥1 bleed during the study.

n=number of subjects (excludes missing data)
sum=number of bleeds
Source: Adapted from BLA 125574/0; Clinical Study Report PH37225, V1.0, Table 9-2

Control of bleeding as measured by the number of injections required to treat a bleed

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. The number of injections per bleed varied between 0 injections and 48 injections

(median 1.0). The majority of bleeds were treated with 1 (70.1%) or 2 (14.5%) injections.
For a summary of these data, see Table 10.

Table 10. Treatment of all bleeds (Part B ITT population)

	CS/EP (N = 111)	CS/ADJ (N = 130)	Combined (N = 241)
No. of injections per bleed			
n	111	130	241
Mean ± SD	1.55 ± 1.54	2.40 ± 5.32	2.01 ± 4.06
Median	1.0	1.0	1.0
[Min; Max]	[0; 11]	[1; 48]	[0; 48]
Sum	172	312	484
No. of bleeds by number of injections [n (%)]			
n	111 (100.0)	130 (100.0)	241 (100.0)
Not treated	4 (3.6)	0	4 (1.7)
1 injection	80 (72.1)	89 (68.5)	169 (70.1)
2 injections	15 (13.5)	20 (15.4)	35 (14.5)
3 injections	5 (4.5)	10 (7.7)	15 (6.2)
>3 injections	7 (6.3)	11 (8.5)	18 (7.5)

n=number of bleeds (excludes missing data)
sum=number of injections
Source: Adapted from BLA 125574/0; Clinical Study Report A62366, V3.0, Table 9-6

Extension part
A total of 315 Kovaltry injections were administered for the treatment of the 154 bleeds. The number of injections per bleed varied between 1 injection and 28 injections (median 1.0). The majority of bleeds were treated with 1 (71.4%) or 2 (14.3%) injections.

For a summary of these data (Part B [only the subjects who enrolled in the extension], extension, and combined), see Table 11.

Table 11. Treatment of all bleeds (Extension ITT population)

	Part B / Year 1 (N = 232)	Extension / Year 2 (N = 154)	Combined / Year 1+2 (N = 386)
No. of injections per bleed			
n	232	154	386
Mean ± SD	2.03 ± 4.13	2.05 ± 3.50	2.04 ± 3.89
Median	1.0	1.0	1.0
[Min; Max]	[0; 48]	[1; 28]	[0; 48]
Sum	471	315	786
No. of bleeds by number of injections [n (%)]			
n	232 (100.0)	154 (100.0)	386 (100.0)
Not treated	4 (1.7)	4 (2.6)	8 (2.1)
1 injection	161 (69.4)	110 (71.4)	271 (70.2)
2 injections	36 (15.5)	22 (14.3)	58 (15.0)
3 injections	14 (6.0)	5 (3.2)	19 (4.9)
>3 injections	17 (7.3)	13 (8.4)	30 (7.8)

n=number of bleeds (excludes missing data)
sum=number of injections
Source: Adapted from BLA 125574/0; Clinical Study Report PH37225, V1.0, Table 9-4

Subject's assessment of response in treatment of bleeds

Part B

The response to treatment of bleeds was done for 235 of the 241 bleeds in total. The response was assessed as "good" or "excellent" in 80.9% (95% CI: 75.2%, 85.7%) of the cases. In 7 of the 235 bleeds (3.0%), the response was assessed as "poor", 2 of these bleeds were successfully treated with 2 injections, 4 with 3 injections, and 1 with 4 injections. Overall, there was a trend towards a better response assessment during the CS/EP period.

For a summary of these data, see Table 12.

Table 12. Response to treatment of bleeds (Part B ITT population)

	CS/EP (N = 111)	CS/ADJ (N = 130)	Total (N = 241)
Response to treatment [n (%)]			
Missing	5	1	6
n	106 (100.0)	129 (100.0)	235 (100.0)
Excellent	31 (29.2)	23 (17.8)	54 (23.0)
Good	64 (60.4)	72 (55.8)	136 (57.9)
Moderate	9 (8.5)	29 (22.5)	38 (16.2)
Poor	2 (1.9)	5 (3.9)	7 (3.0)

Source: Original from BLA 125574/0; Clinical Study Report A62366, V3.0, Table 9-8

Extension part

The response to treatment of bleeds was assessed for 149 of the 150 treated bleeds in total (see Table 13). The response was assessed as "good" or "excellent" in 71.8% (95% CI: 63.9%, 78.9%) of the cases. In 8 of the bleeds (5.4%), the response was assessed as "poor".

Table 13. Response to treatment of bleeds (Extension ITT population)

	Part B / Year 1 (N = 232)	Extension / Year 2 (N = 154)	Combined / Year 1+2 (N = 386)
Response to treatment [n (%)]			
Missing	6	5	11
n	226 (100.0)	149 (100.0)	375 (100.0)
Excellent	54 (23.9)	37 (24.8)	91 (24.3)
Good	129 (57.1)	70 (47.0)	199 (53.1)
Moderate	36 (15.9)	34 (22.8)	70 (18.7)
Poor	7 (3.1)	8 (5.4)	15 (4.0)

Source: Original from BLA 125574/0; Clinical Study Report PH37225, V1.0, Table 9-6
N/n=number of bleeds

Hemostatic outcome of surgeries

See integrated overview of efficacy in section 7.2.

6.1.11.3 Subpopulation Analyses

The results of the subgroup analysis showed that the median ABR (total bleeds) was higher in children (12 to 17 years) than in adults (median: 2.83 bleeds/year vs.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).

Evaluation of the influence of injection frequency revealed a lower ABR in the more frequent dosing cohort (2x per week: 1.02 bleeds/year vs. 3x per week: 2.02 bleeds/year; median values).

The results of the subgroup analysis by region indicated higher ABR (mean: 5.45 bleeds/year; median: 3.95 bleeds/year) in South Africa than the ABR in other regions.

A summary of the results is shown in Table 14.

Table 14. Annualized number of total bleeds for selected subgroups (Part B ITT population)

	Combined analysis (N = 62) Subgroups	
Age group	**Children (12-17 years)**	**Adults (≥ 18 years)**
n	10	52
Mean ± SD	6.38 ± 8.47	3.30 ± 4.28
Median	2.83	1.02
[Q1; Q3]	[0.00; 10.80]	[0.00; 4.50]
Treatment schedule during Part B	**2x per week**	**3x per week**
n	18	44
Mean ± SD	4.77 ± 7.61	3.39 ± 3.89
Median	1.02	2.02
[Q1; Q3]	[0.00; 8.03]	[0.46; 5.01]
Prior treatment	**On-demand**	**Prophylaxis**
n	12	50
Mean ± SD	4.32 ± 5.31	3.67 ± 5.23
Median	1.99	1.03
[Q1; Q3]	[0.49; 7.46]	[0.00; 5.09]
Region	**Europe**	**Israel**
n	31	18
Mean ± SD	4.45 ± 6.32	2.45 ± 2.91
Median	1.05	1.02
[Q1; Q3]	[0.00; 7.18]	[0.98; 3.05]
	United States of America	**South Africa**
n	7	6
Mean ± SD	2.91± 4.11	5.45 ± 5.43
Median	0.93	3.95
[Q1; Q3]	[0.00; 5.99]	[0.98; 9.98]

Source: Adapted from BLA 125574/0; Clinical Study Report A62366, V3.0, Table 9-3

The applicant also performed the subgroup analysis of ABR by race. Three race groups and one uncodable race group are represented in the study. However, the number of subjects for non-white race groups is small. The median and mean ABRs in non-white are higher than the respective ABRs in White (median: 2.65 vs. 1.02; mean: 5.33 vs. 3.60) (Table 15).

Table 15. Annualized bleeding rate by race and treatment regimen (ITT population)

		CS/EP	CS/ADJ	Combined
WHITE	n	55	55	55
	Mean	3.24	3.88	3.60
	SD	5.20	5.90	5.13
	Min	0.0	0.0	0.0
	Q1	0.00	0.00	0.00
	Median	1.90	1.88	1.02
	Q3	4.08	7.34	4.93
	Max	22.8	29.1	26.1
NON-WHITE	n	7	6	7
	Mean	5.19	6.26	5.33
	SD	5.99	8.64	6.01
	Min	0.0	0.0	0.0
	Q1	0.00	0.00	0.00
	Median	4.57	2.96	2.65
	Q3	10.20	9.77	10.80
	Max	15.6	21.9	13.9

Source: Adapted from BLA 125574/0; Clinical Study Report A62366, V3.0, Table 14.2/3

6.1.12 Safety Analyses

6.1.12.3 Deaths

No subject died during the study (Part A, B or C).

6.1.12.4 Nonfatal Serious Adverse Events (SAE)

Six subjects each experienced at least one SAE: one subject in the interval between first and second PK session in Part A, one subject during the screening period of Part B, three subjects during treatment in Part B, and one subject during treatment in Part C.

None of the SAEs was rated as drug-related and all SAEs had resolved or improved by the end of the observation period.

The information for all SAEs is shown in Table 16.

Table 16. Listing of all SAEs in Part A, Part B and Part C (all subjects)

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: Original from BLA 125574/0; Clinical Study Report A62366, V3.0, Table 10-9

6.2 Trial #2: Leopold II (Protocol 14319)

Leopold II study is titled "A phase II/III, randomized, cross-over, open-label trial to demonstrate superiority of prophylaxis over on-demand therapy in previously treated subjects with severe hemophilia A treated with plasma protein-free recombinant FVIII formulated with sucrose (Kovaltry)."

6.2.1 Objectives (Primary, Secondary, etc.)

Primary objective:

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

Secondary objectives:

- To demonstrate superiority of prophylaxis versus on-demand treatment with Kovaltry (dose determined by CS/EP) as measured by bleeding rate.
- To demonstrate superiority of prophylaxis versus on-demand treatment with Kovaltry (dose determined by CS/ADJ) as measured by bleeding rate.
- To demonstrate the non-inferiority of Kovaltry dose determined by CS/EP versus Kovaltry dose determined by CS/ADJ as measured by the proportion of bleeds controlled by ≤ 2 injections (among all bleeds) in subjects treated on demand. This objective is reviewed in Section 7.1.

Other objectives:

- To compare bleeding frequency during prophylaxis treatment with Kovaltry (dose determined by CS/EP versus dose determined by CS/ADJ) as measured by the bleeding rate.
- To compare bleeding frequency during prophylaxis treatment with Kovaltry (low-dose Kovaltry versus high-dose Kovaltry) as measured by the bleeding rate.
- 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.
- 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.
- To evaluate the potential for antibody formation to HSP70 and/or hamster proteins during Kovaltry treatment.
- To evaluate the potential for inhibitory antibody formation to Kovaltry during study treatment.
- To evaluate all surgical outcomes during treatment with Kovaltry.
- To assess health-related QoL and pharmaco- economic parameters during treatment with Kovaltry.

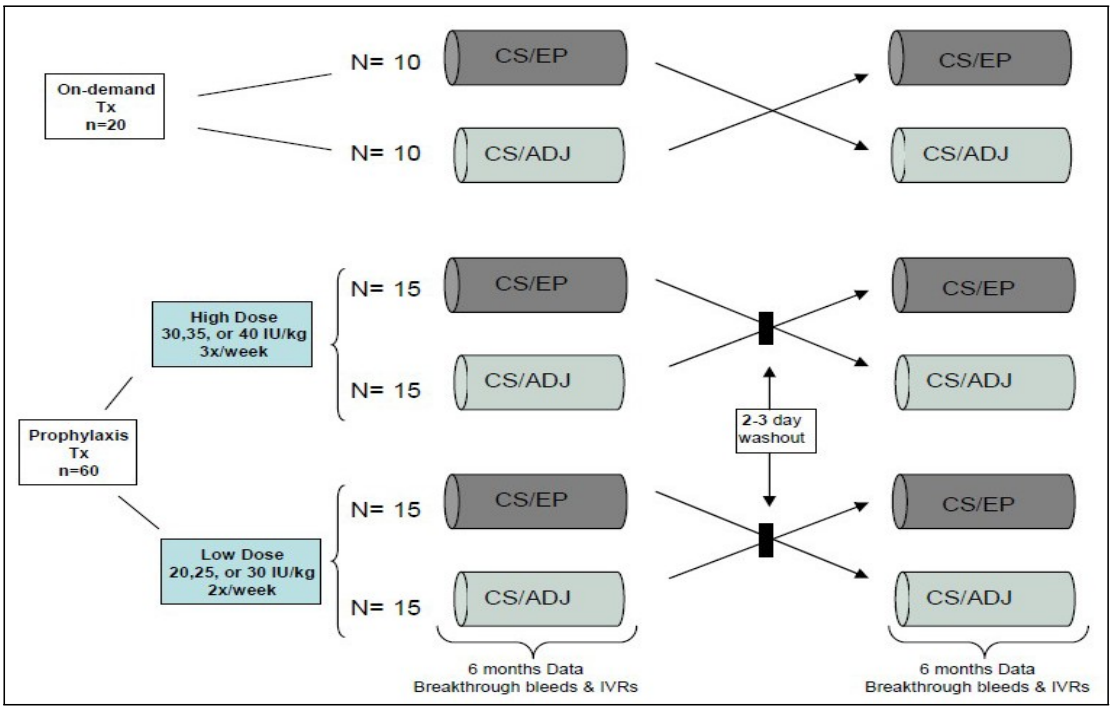
6.2.2 Design Overview

This was a Phase-II/III, randomized, multicenter, open-label, intra-individual, cross-over study in subjects diagnosed with severe hemophilia A.

Eighty subjects were to be randomized to one of six treatment arms (see Figure 2), where the two treatment periods for each treatment arm was defined by the type of potency assignment (CS/EP or CS/ADJ). All subjects in the six arms were to undergo either prophylaxis or on-demand treatment for a period of 6-months. Subjects then crossed-over (within their respective treatment arm) to the alternate potency assignment for a 6-month treatment period. Subjects in the prophylaxis treatment

arms underwent a 2-3 day washout period before progressing to the second 6-month treatment period.

Figure2. Study design



CS/ADJ = Chromogenic substrate assay/label adjusted to mimic one-stage assay
CS/EP = Chromogenic assay per European Pharmacopoeia
IVR = *In vivo* recovery
Tx = Treatment
Source: Original from BLA 125574/0; Clinical Study Report PH37042, V2.0, Figure 7-1

Pre-medications were not to be administered for injections of Kovaltry. If pre-medications were contemplated, this was to be discussed on a case-by-case basis with the Bayer Medical Expert before administration. The only exception to the use of other FVIII products was for surgery, if needed before the approval by the DMC of the use of Kovaltry in a surgical setting.

6.2.3 Population

Subject eligibility criteria:

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 ED in total with any rFVIII or pdFVIII 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 BU/mL] in two 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 two 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 one occasion but with at least three subsequent successive negative results (<0.6 BU) thereafter were also eligible.
7. Willingness and ability to complete training in the use of the study 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.

6.2.4 Study Treatments

Prophylaxis and on-demand treatment

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. The specific dose per injection for each subject was to be selected by the investigator. Once a subject had been assigned a certain prophylaxis dose, the assignment was to be maintained for the duration of the study.
Dosage for on-demand treatment:	The dosage was to be adjusted to bleeding location and severity and to current standard care.

In all groups, potency assignments were labeled according to either CS/EP or CS/ADJ results, depending on the order of randomization.

Treatment during surgery

Kovaltry was not supplied for use in the surgical setting until at least 20 bleeding events had been assessed, to ensure the hemostatic activity of Kovaltry. All sites were

informed by the applicant when surgical treatment using Kovaltry was allowed to commence.

6.2.6 Sites and Centers

The study was conducted at 30 study centers in 11 countries (number of recruiting sites in parentheses): China (5), Czech Republic (1), Japan (4), Mexico (2), Romania (4), Republic of Serbia (4), Russia (2), South Africa (2), Taiwan (1), Turkey (3) and US (2).

6.2.8 Endpoints and Criteria for Study Success

Primary efficacy variable: ABR for all bleeds in the combined CS/EP and CS/ADJ periods. The null hypothesis is that the ABRs are equal for the on-demand subjects and the prophylactic subjects. The alternative hypothesis is that they are not equal. A p-value ≤ 0.05 would reject the null hypothesis.

Secondary efficacy variables:

- ABR for all bleeds in the CS/EP period.
- ABR for all bleeds in the CS/ADJ period.
- Proportion of bleeds controlled by ≤ 2 injections among all bleeds (also included untreated bleeds) in subjects treated on demand in the CS/EP period and the CS/ADJ period.

Other efficacy variables:

- Number of bleeds.
- FVIII recovery values.
- FVIII usage calculation expressed as number of injections, number of prophylaxis injections, and dose per injection.
- 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.
- Subject's assessment of response to treatment
- Hemostatic outcome of surgeries
- Change in QoL

6.2.9 Statistical Considerations & Statistical Analysis Plan

Analysis populations

Safety population:	All subjects randomized into the study who received at least one injection of Kovaltry.
ITT population:	All subjects in the safety population who have injection /bleeding data from the EPD and/or CRF.
PP population:	All subjects in the ITT population who have no major protocol deviations and have EPD data from both crossover periods.

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

Subgroup analyses

The subgroup analyses planned for the primary efficacy variable included:

- Children (age <18 years) / adults (age ≥18 years)
- Age group (<18 years, ≥18 to <30 years, ≥30 years)
- Asia / non-Asia [note: Asia was defined as from China, Taiwan, or Japan (not by race)]

Sample size determination

Assuming that subjects treated with prophylaxis would have an average of 5 bleeds per year and that subjects treated on demand would have an average of 15 bleeds per year with a combined standard deviation of 11 bleeds per year, then using a two-sided alpha level of 0.05, 90% power, an attrition rate of 15%, and a 3:1 ratio of subjects treated with prophylaxis to subjects treated on demand, a sample size of 60:20 subjects (prophylaxis: on-demand) was required.

Handling of missing data

If dates for bleeds and infusions are both missing then these bleeds/infusions cannot be counted. Each subject's period start and stop date were to be needed to compute the ABR. If the bleed date is missing, but the infusion date is available, the infusion date was to be used. If the details of a bleed are missing (e.g. type of bleed: spontaneous-trauma), the bleed was to be counted for all bleeds, but not for the subgroup of spontaneous or trauma bleeds.

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. Other efficacy variables and all safety variables were planned to be analyzed using summary statistics. The number of data available and missing data, mean, standard deviation, median, minimum and maximum values and other summary statistics were to be calculated for continuous data. Frequency tables were to be generated for categorical data.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

All of the 80 treated subjects (21 in the on-demand group and 59 in the prophylaxis groups) were included in the ITT and safety populations (Table 17). With the exception of the subject treated on-demand who discontinued the study due to non-compliance with the documentation of dosing, all subjects (n=79) were valid for PP analysis.

Table 17. Analysis sets (all treated subjects)

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

6.2.10.1.1 Demographics

The ITT/safety population consisted of 80 male subjects, aged between 14 and 59 years (median: 28.5 years). Ten subjects (12.5%) were adolescents between 14 and 16 years. The majority of subjects were either of White (45.0%) or Asian (40.0%) race and had a normal BMI (mean: 21.83 ± 3.95 kg/m^2). There were no relevant differences between the on-demand and the prophylaxis groups.A summary of the demographic and other baseline characteristics is shown in Table 18.

Table 18. Demographic and other baseline characteristics (ITT/safety population)

	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

For 79 subjects (one subject had the confirmation only at baseline before the first injection), severe hemophilia A was confirmed at Screening by the central lab with FVIII:C < 1% . Sixty of the 80 treated subjects had a FVIII:C <1% documented in medical history.

Seventy-seven of 80 subjects (96.3%) had documentation of previous bleeds. In these subjects, the median number of bleeds in the previous year was 36.0 (range: 3 to 106 bleeds) and about 2/3 of these bleeds were joint bleeds. Ninety percent of

the subjects (72 out of 80) had target joints for bleeds and the number of target joints ranged between 0 and 9 (median: 3.0).

There were no relevant differences among the treatment groups with regard to disease characteristics at Baseline. A summary of these data is shown in Table 19.

Table 19. Disease characteristics at Baseline (ITT/safety population)

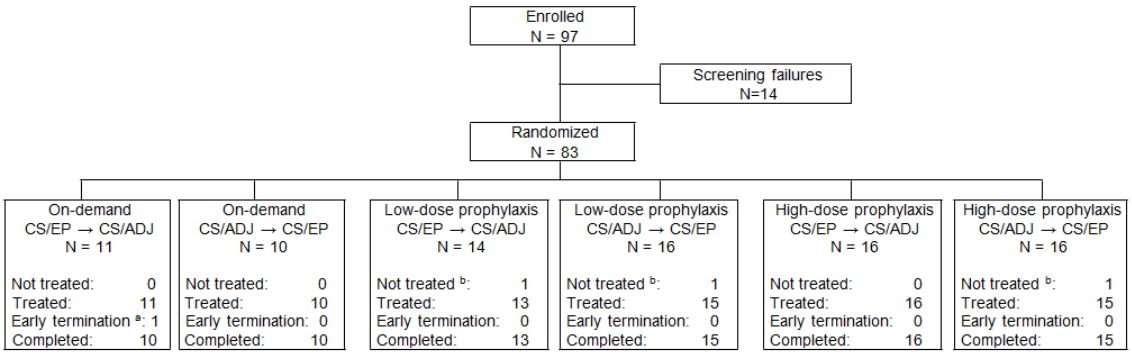
	On-demand (N = 21)	Low-dose Prophylaxis (N = 28)	High-dose Prophylaxis (N = 31)	Total (N = 80)
Target joint for bleeds [n (%)]				
missing	0 (0.0)	0 (0.0)	1 (3.2)	1 (1.3)
no	2 (9.5)	3 (10.7)	2 (6.5)	7 (8.8)
yes	19 (90.5)	25 (89.3)	28 (90.3)	72 (90.0)
Number of target joints				
n	21	28	30	79
Mean ± SD	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

Figure 3 gives an overview on the subject disposition in this study.

Figure 3. Subject disposition (all subjects)



[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

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary and Secondary 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 59.96 bleeds/year and 1.98 bleeds/year, respectively. Comparison of the ABRs in an ANOVA resulted in p<0.0001, therefore the primary objective of this study was met. Similar results were seen in both secondary comparisons considering the bleeding rates during the CS/EP and CS/ADJ periods separately.

A summary of the ABRs and their comparisons are given in Table 20 and Table 21.

Table 20. Annualized number of bleeds: on-demand and prophylaxis treatment with Kovaltry (ITT population)

	Potency / dose	Annualized number of bleeds			
		N	Mean ± SD	Median	[Q1; Q3]
Primary variable					
On-demand	All combined	21	57.69 ± 24.56	59.96	[41.74; 76.32]
Prophylaxis	All combined	59	4.94 ± 6.81	1.98	[0.00; 7.03]
Secondary variables					
On-demand	CS/EP	21	57.61 ± 24.26	59.55	[39.38; 72.68]
Prophylaxis	CS/EP combined [a]	59	5.11 ± 7.95	2.03	[0.00; 6.78]
On-demand	CS/ADJ	20	59.73 ± 25.06	59.12	[40.98; 77.84]
Prophylaxis	CS/ADJ combined [a]	59	4.77 ± 6.79	2.00	[0.00; 7.78]

Q1 = 25% quartile; Q3 = 75% quartile.
[a] High-dose and low-dose prophylaxis combined
Source: Adapted from BLA 125574/0; Clinical Study Report PH37042, V2.0, Table 9-1

Table 21. Comparison of the annualized number of bleeds: on-demand versus prophylaxis treatment with Kovaltry (ITT population)

Treatment Comparison			p-value for the treatment difference (ANOVA)
Primary comparison			
On-demand (combined [b])	vs.	Prophylaxis (all combined)	< 0.0001
Secondary comparisons			
On-demand CS/EP	vs.	Prophylaxis CS/EP (combined [a])	< 0.0001
On-demand CS/ADJ	vs.	Prophylaxis CS/ADJ (combined [a])	< 0.0001

[a] High-dose and low-dose prophylaxis combined
[b] CS/EP and CS/ADJ periods combined
Source: Original from BLA 125574/0; Clinical Study Report PH37042, V2.0, Table 9-2

Supportive analyses

Excluding subjects from sites 54005 and 54001

The findings of the EMA inspections of China sites 54005 and 54001 for the Leopold II study identified substantial deviation from the study protocol and inadequate documentation of medical history. These findings raised concern for the FDA with regard to study conduct at these sites; therefore the FDA requested the applicant to perform sensitivity analysis for the primary efficacy endpoint by excluding the subjects from sites 54005 and 54001.

Table 22 shows the analysis results with and without the nine subjects from Sites 54005 and 54001. The median ABR for the on-demand group decreased from 60.0 bleeds/year to 52.0 bleeds/year. No other substantial impact was seen after excluding the nine subjects.

Table 22. Bleeds per year (median, Q1 and Q3), total population and excluding 9 subjects from Sites 54001 and 54005 (ITT population)

	On Demand	2x/week (Low-Dose) Prophylaxis	3x/week (High-Dose) Prophylaxis	Prophylaxis Combined
All subjects, N	**21**	**28**	**31**	**59**
Total bleeds per year Median (Q1; Q3)	60.0 (41.7; 76.3)	4.0 (0; 8.0)	2.0 (0; 4.9)	2.0 (0; 7.0)
Total subjects after excluding 9 subjects, N	**19**	**24**	**28**	**52**
Total bleeds per year Median (Q1; Q3)	52 (37.1; 76.3)	4.0 (0; 9.6)	2.0 (1.0; 6.0)	2.0 (0.5; 7.0)

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

Poisson regression

As requested by the FDA, the applicant provided the sensitivity analyses for the comparison of the ABR between on-demand and prophylaxis treatment with Kovaltry using Poisson regression.

As shown in Table 23, the primary comparison resulted in estimated ABRs of 4.95 (95% CI: 3.57, 6.89) for prophylaxis (n=59) versus 59.06 (95% CI: 50.21, 69.47) for on-demand (n=21). The percent reduction of prophylaxis over on-demand arms in ABR was 91.6% (95% CI: 87.9%, 94.2%). The lower limit of the 95% CI was much higher than 50%. Similar results were seen in the secondary comparisons considering the bleeding rates during the CS/EP and CS/ADJ periods separately. Compared to the results using ANOVA, Poisson regression yields similar results.

Table 23. Comparison of ABRs for prophylaxis versus on-demand using Poisson regression (ITT population)

Comparison	n	ABR (95% CI)	Rate ratio (95%)	% reduction (95% CI)	p-value
On-demand (all combined [b])	21	59.06 (50.21, 69.47)			< 0.0001
Prophylaxis (all combined [a,b])	59	4.95 (3.57, 6.89)	0.08 (0.06, 0.12)	91.6 (87.9, 94.2)	
On-demand CS/EP	21	58.49 (49.10, 69.67)			< 0.0001
Prophylaxis CS/EP (combined [a])	59	5.14 (3.63, 7.30)	0.09 (0.06, 0.13)	91.2 (87.0, 94.0)	
On-demand CS/ADJ	20	59.66 (50.27, 70.79)			< 0.0001
Prophylaxis CS/ADJ (combined [a])	59	4.77 (3.35, 6.78)	0.08 (0.05, 0.12)	92.0 (88.2, 94.6)	

a high-dose and low-dose prophylaxis combined

Rate ratios and percent reduction are prophylaxis versus on-demand. Estimates and p-values are derived from Poisson regression model considering over-dispersion and including an offset variable to account for different follow-up times.

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

Excluding the nine subjects from sites 54001 and 54005 has no substantial impact on the Poisson regression results. The primary comparison resulted in estimated ABRs of 5.30 (95% CI: 3.77, 7.46) for prophylaxis (n=19) versus 56.56 (95% CI: 47.42, 67.46)

for on-demand (n=52). The percent reduction in ABRs is 90.6% (95% CI: 86.2%, 93.6%) for prophylaxis versus on demand (see Table 24).

Table 24. Comparison of ABRs for prophylaxis versus on-demand using Poisson Regression, excluding 9 subjects from sites 54001 and 54005 (ITT population)

Comparison	n	ABR (95% CI)	Rate ratio (95%)	% reduction (95% CI)	p-value
On-demand (all combined [b])	19	56.56 (47.42, 67.46)			< 0.0001
Prophylaxis (all combined [a,b])	52	5.30 (3.77, 7.46)	0.09 (0.06, 0.14)	90.6 (86.2, 93.6)	
On-demand CS/EP	19	55.65 (45.95, 67.40)			< 0.0001
Prophylaxis CS/EP (combined [a])	52	5.52 (3.84, 7.95)	0.10 (0.07, 0.15)	90.1 (85.0, 93.4)	
On-demand CS/ADJ	18	57.50 (47.80, 69.17)			< 0.0001
Prophylaxis CS/ADJ (combined [a])	52	5.08 (3.52 , 7.33)	0.09 (0.06, 0.13)	91.2 (86.7, 94.1)	

a high-dose and low-dose prophylaxis combined
Rate ratios and percent reduction are prophylaxis versus on-demand. Estimates and p-values are derived from Poisson regression model considering over-dispersion and including an offset variable to account for different follow-up times.
Source: Bayer's response to late-cycle meeting package, dated October 28, 2015

6.2.11.2 Analyses of Other Endpoints

Number of bleeds

None of the subjects in the on-demand group, but 16 subjects (27.1%) in the prophylaxis group remained bleed-free during the study.

The median ABR of **spontaneous bleeds** was 42.09 bleeds/year in the on- demand group and 0.99 bleeds/year in the prophylaxis group, whereby it was higher in the low-dose than in the high-dose group (2.01 vs. 0 bleeds/year). The ABR of **joint bleeds** was much lower during prophylaxis than during on-demand treatment (1.97 bleeds/year vs. 38.76 bleeds/year).

Table 25 summarizes these data for the ITT population.

Table 25. Summary of bleeds during on-demand and prophylaxis treatment (ITT population)

	On-demand	Prophylaxis		
	Combined N = 21	Low dose N = 28	High dose N = 31	Combined N = 59
No. of spontaneous bleeds per year				
n	21	28	31	59
Mean ± SD	45.30 ± 22.06	4.52 ± 7.07	2.62 ± 4.90	3.52 ± 6.05
Median	42.09	2.01	0.00	0.99
[Q1; Q3]	[24.3; 61.3]	[0.0; 6.5]	[0.0; 3.0]	[0.0; 4.0]
Number of trauma bleeds per year				
n	21	28	31	59
Mean ± SD	12.25 ± 16.35	0.93 ± 1.49	1.54 ± 2.81	1.25 ± 2.28
Median	8.11	0.00	0.98	0.00
[Q1; Q3]	[1.0; 15.0]	[0.0; 1.0]	[0.0; 2.0]	[0.0; 2.0]
Number of joint bleeds per year				
n	21	28	31	59
Mean ± SD	43.84 ± 24.71	5.16 ± 6.92	3.53 ± 6.15	4.30 ± 6.52
Median	38.76	2.52	1.01	1.97
[Q1; Q3]	[24.3; 60.0]	[0.0; 7.5]	[0.0; 4.0]	[0.0; 6.0]
Time to first bleed in period [days] [b]				
n	21	20	23	43
Mean ± SD	4.99 ± 5.25	41.49 ± 41.33	59.58 ± 46.36	51.16 ± 44.52
Median	3.08	31.26	48.04	40.27
[Q1; Q3]	[1.0; 8.0]	[9.2; 60.7]	[27.5; 87.3]	[12.5; 67.9]

[b] Only subjects with at least 1 bleed.

Source: Adapted from BLA 125574/0; Clinical Study Report PH37042, V2.0, Table 9-3

FVIII dose per injection

The median dose per injection was lower in the on-demand group than in the prophylaxis group (22.03 [range 11 to 35] vs. 29.41 [range 19 to 49] IU/kg/injection).

Description of bleeding according to location and frequency of all bleeds, joint bleeds, spontaneous bleeds and trauma bleeds

A total of 1497 bleeds occurred in the ITT population (1204 in the on-demand group and 293 in the prophylaxis group). Respectively, 78.5% and 73.9% of these bleeds were spontaneous bleeds in the on-demand group and in the prophylaxis group. 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 104 (8.7%) severe bleeds were reported in subjects in the on-demand group and 33 (11.3%) in subjects in the prophylaxis group. The remaining bleeds were rated as either mild (30.7% in the on-demand group and 41.0% in the prophylaxis group) or moderate (60.6% in the on-demand group and 47.8% in the prophylaxis group).

A summary of the characteristics of bleeds is shown in Table 26.

Table 26. Characteristics of bleeds during treatment with Kovaltry (ITT population)

	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)
Target joint bleed [n (%)]				
n	868 (100.0)	141 (100.0)	105 (100.0)	246 (100.0)
Yes	661 (76.2)	102 (72.3)	82 (78.1)	184 (74.8)
Bleeding severity [n (%)]				
Missing	8	0	0	0
n	1196 (100.0)	160 (100.0)	133 (100.0)	293 (100.0)
Mild	367 (30.7)	60 (37.5)	60 (45.1)	120 (41.0)
Moderate	725 (60.6)	90 (56.3)	50 (37.6)	140 (47.8)
Severe	104 (8.7)	10 (6.3)	23 (17.3)	33 (11.3)

Source: Adapted from BLA 125574/0; Clinical Study Report PH37042, V2.0, Table 9-4

Control of bleeding as measured by the number of injections required to treat a bleed

A total of 1607 Kovaltry injections were administered for the on-demand group and 352 for the prophylaxis group. The vast majority of bleeds were successfully treated with 1 or 2 injections (95.3% in the on-demand group and 96.2% in the prophylaxis group). A summary of the treatment of bleeds is shown in Table 27.

Table 27. Treatment of bleeds with Kovaltry (ITT population)

	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
n=number of bleeds (excludes missing data)
sum=number of injections
Source: Original from BLA 125574/0; Clinical Study Report PH37042, V2.0, Table 9-5

Subject's assessment of response to treatment

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) (95% CI: 65.7%, 70.5%) of the bleeds. In 28 bleeds (1.9%), the response was assessed as "poor".

For a summary of these data, see Table 28.

Table 28. Response to treatment of bleeds (ITT population)

	On-demand	Prophylaxis		
	Combined N = 1204	Low dose N = 160	High dose N = 133	Combined N = 293
Response to treatment [n (%)]				
Missing	8	12	2	14
n	1196 (100.0)	148 (100.0)	131 (100.0)	279 (100.0)
Excellent or good	834 (69.7)	83 (56.1)	89 (67.9)	172 (61.6)
Excellent	335 (28.0)	34 (23.0)	14 (10.7)	48 (17.2)
Good	499 (41.7)	49 (33.1)	75 (57.3)	124 (44.4)
Moderate	346 (28.9)	55 (37.2)	40 (30.5)	95 (34.1)
Poor	16 (1.3)	10 (6.8)	2 (1.5)	12 (4.3)

Source: Original from BLA 125574/0; Clinical Study Report PH37042, V2.0, Table 9-8

Hemostatic outcome of surgeries

See integrated overview of efficacy in section 7.2.

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 is approximately twice the median ABR in >=30 age group for the adults in prophylaxis treatment (4.53 vs. 1.96). The results of these analyses are displayed in Table 29.

Table 29. Annualized number of bleeds for selected subgroups: on-demand and prophylaxis treatment with Kovaltry (ITT population)

	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

As requested in the late-cycle meeting by the FDA, the applicant performed the subgroup analysis of ABR by race. Four race groups are represented in the study, however, the number of black and Hispanic subjects are small. The median and mean

ABRs in white subjects are higher than the respective ABRs in Asian subjects (median: 2.5 vs. 2.0; mean: 5.7 vs. 4.4) during prophylaxis (Table 30).

Table 30. Annualized bleeding rate by race and treatment regimen (ITT population)

Secondary objectives:

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

6.3.2 Design Overview

This is a phase-III, multicenter, open-label, uncontrolled study to demonstrate the safety and efficacy of the treatment with Kovaltry for prophylaxis, breakthrough bleeds, and surgery in children with severe hemophilia A.

The study is divided into two parts: Part A (completed) was to investigate a total of 50 PTPs ≤12 years of age. Part B (ongoing) is to include at least 25 PUPs. All subjects in Part A and Part B are to receive prophylaxis treatment with Kovaltry. Subjects in Part A were to be treated at least 2x/week, or more frequently, as needed, and subjects in Part B were at least 1x/week, or with the subject's first bleeding event.

Part A was to start after 20 adult/adolescent subjects had 50 EDs each with Kovaltry without safety concerns in previous studies with BAY 81- 8973. PTPs aged 6 to 12 years were to begin enrollment first, followed by PTPs <6 years. Part B, for PUPs, was to begin enrollment after 20 children in Part A had accumulated 50 ED each.

The total study duration (including screening period) per subject in Part A was to be approximately 6-8 months, during which time the subjects were to accumulate at least 50 EDs each. For Part B, subjects were to continue in the study until achieving 50 ED. All subjects in both Parts were to be offered participation in an open-label extension study for an additional 6-12 months to allow observations for ≥100 EDs or until marketing authorization is obtained.

Pre-medications to tolerate treatment with Kovaltry were not allowed. Use of topical anesthetics prior to venipuncture was permitted. PTPs were to continue their previous treatment up to 48 hours before the first dose of Kovaltry. All medications and blood products required by the subject during the study were to be listed in the CRF. Subjects were to take no other experimental drugs during their participation in this study.

Since Part B and the extension parts are still ongoing, the CSR submitted by the applicant only presented the results of the 6-month Part A study (in PTPs). Hence this review will only include relevant study contents for Part A, and the limited safety update for Part B submitted in amendment 42 on August 31, 2015, amendment 29 on September 2, 2015, and amendment 42 on January 22, 2016

6.3.3 Population

Subject eligibility criteria:

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.

4. No current evidence of inhibitor antibody measured using the Nijmegen-modified Bethesda assay [<0.6 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 EPD and to document injections during the study.
7. Written informed consent by parent/legal representative. Assent should be sought from subjects if appropriate.

6.3.4 Study Treatments

Regular prophylaxis

Route of administration: Manual intravenous (IV) injection over 1 – 15 minutes.
Dosage: PTPs: 25 – 50 IU/kg, ≥2x/week

Treatment of breakthrough bleeds and surgery

The dosage of Kovaltry was to be at the discretion of the investigator.

Immune tolerance induction

In the event of inhibitor development, subjects were to be treated with an immune tolerance induction therapy regimen with Kovaltry at an initial dose of 200 IU/kg per day, either once a day or 100 IU/kg twice a day at the investigator's discretion until successful eradication of the inhibitor, or until failure, for a maximum of 18 months.

6.3.6 Sites and Centers

The study was conducted in 25 study centers in 12 countries (number of recruiting sites in parenthesis): Bulgaria (2), Canada (2), Denmark (1), Hungary (3), Ireland (1), Israel (1), Italy (3), Latvia (1), Lithuania (1), Poland (3), Romania (3), US (4).

6.3.8 Endpoints and Criteria for Study Success

Primary efficacy variable:
ABR of total bleeds during prophylaxis treatment that occur within 48 hours after the previous prophylaxis injection.

ABR under prophylaxis =
(# 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
- last datetime in study is the later of the date of Visit 6 (assume time of visit is noon) or last datetime in the EPD 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 (Excellent: perioperative blood loss similar to the non-hemophilic patient; Good: perioperative bleeding slightly

but not clinically significantly increased over expectations for the non-hemophilic patient. Treatment similar to non-hemophilic patient).
- 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

Analysis populations

Safety population:	All subjects who entered the study and received at least one injection of Kovaltry.
ITT population:	All subjects in the safety population who have injection/bleeding data from the EPD.
PP population:	All subjects in the ITT population who have no major protocol deviations and have data from the EPD.

The ITT population was to be used for the primary efficacy analysis. The efficacy analysis of the PP population was to be considered supportive. The PP population was used for the primary analysis of the FVIII recovery data.

Subgroup analysis

The subgroups planned for the analysis of the ABR within 48 hours after prophylaxis and at any time during prophylaxis treatment included:
- Prophylaxis Treatment regimen (≤2x/week, >2x/week)
- Average prophylaxis dose high (≥30 IU/kg), low dose (<30 IU/kg)
- Race group (white, non-white)
- Region (North America, Europe, Israel)

Sample size determination

Sample size was determined according to the requirements by guideline Clinical Investigation of Medicinal Products in the Pediatric Population (CPMP)/BPWG/1561/99 (Note for Guidance on the Clinical Investigation of Recombinant Factor VIII and Factor IX Products), and taking into account the revised draft version, CHMP/BPWP/144533/09. Age groups are in accordance with the International Conference on Harmonization /CPMP guideline E11.

This pediatric study consisted of two parts. Part A was to include a total of 50 PTPs; 25 subjects aged >6 - 12 years and 25 subjects aged 0 - 6 years.

Handling of missing data

Each subject's start and stop date were needed to compute the ABR. If a bleed date is missing, but an infusion date is available, infusion date was to be used as the bleed date. When computing age at diagnosis, age at start of therapy, and time since start of therapy: use 15 if day is missing, and use July 1 if month and day are missing. If necessary, adjust imputed dates so they are not before the birth date.

Statistical methodology

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

6.3.10.1 Populations Enrolled/Analyzed

All of the 51 enrolled and treated subjects were valid for safety and ITT analysis (see Table 32). All but 1 subject were included in the PP population due to a major protocol deviation (Subject (b) (6) in the age group 6-12 years has a treatment interruption of more than 14 days.).

Table 32. Analysis sets of Part A (all subjects)

Analysis set	PTPs 0 – <6 years (N = 25)	PTPs 6 – 12 years (N = 26)	PTPs Total (N = 51)
Safety population	25	26	51
ITT population	25	26	51
PP population	25	25	50
PK analysis population	3	9	12

Source: Original from BLA 125574/0; Clinical Study Report A51496, V2.0, Table 8-1

6.3.10.1.1 Demographics

The ITT/safety population consisted of 51 male subjects, aged between 1 and 11 years. The median age in the younger age group was 4 years and in the older age group it was 9 years. The majority of subjects (94.1%, 48/51) were of White race. A summary of the demographic and other baseline characteristics is shown in Table 33.

Table 33. Demographic and other baseline characteristics (ITT/safety population)

	PTPs 0 – <6 years (N = 25)	PTPs 6 – 12 years (N = 26)	PTPs Total (N = 51)
Sex [n (%)]			
Male	25 (100.0)	26 (100.0)	51 (100.0)
Age (years)			
n	25	26	51
Mean ± SD	3.8 ± 1.3	8.8 ± 1.8	6.4 ± 3.0
Median	4.0	9.0	6.0
[Min; Max]	[1; 5]	[6; 11]	[1; 11]
Race			
White	24 (96.0)	24 (92.3)	48 (94.1)
Black	1 (4.0)	2 (7.7)	3 (5.9)
Ethnicity			
Not Hispanic or Latino	23 (92.0)	25 (96.2)	48 (94.1)
Hispanic or Latino	1 (4.0)	0 (0.0)	1 (2.0)
Not reported	1 (4.0)	1 (3.8)	2 (3.9)
Baseline height (cm)			
n	25	26	51
Mean ± SD	108.3 ± 12.9	138.2 ± 13.8	123.5 ± 20.1
Median	114.0	138.5	123.0
[Min; Max]	[74; 126]	[109; 168]	[74; 168]
Baseline weight (kg)			
n	25	26	51
Mean ± SD	19.0 ± 5.3	32.4 ± 10.4	25.8 ± 10.7
Median	18.5	29.0	22.6
[Min; Max]	[11; 39]	[17; 59]	[11; 59]
Baseline BMI (kg/m^2)			
n	25	26	51
Mean ± SD	16.1 ± 2.5	16.5 ± 2.6	16.3 ± 2.6
Median	15.1	16.1	15.7
[Min; Max]	[13; 24]	[13; 24]	[13; 24]

Abbreviation: SD = standard deviation
Note: The youngest subject was 16 months when it received the first infusion in the study.
Source: Original from BLA 125574/0; Clinical Study Report A51496, V2.0, Table 8-2

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The number of bleeds in the year prior to study entry ranged from 0 to 55 (median: 4.0). The percentage of subjects with target joints was lower in the younger age group (20.0% vs. 34.6% in the older age group). The maximum number of four target joints was present in a subject in the older age group.

Eleven subjects (21.6%) received on demand treatment and 40 subjects (78.4%) received regular prophylaxis with a FVIII product prior to the study. Of these 40 subjects, 92% (23 out of 25) were in the younger age group and 65.4% (17 out of 26) were in the older age group.

A summary of disease characteristics of the ITT/safety population is shown in Table 34.

Table 34. Disease characteristics at Baseline (ITT/safety population)

	PTPs 0 – <6 years (N = 25)	PTPs 6 – 12 years (N = 26)	PTPs Total (N = 51)
No. of bleeds in the last 12 months			
n	25	26	51
Mean ± SD	7.3 ± 12.0	8.5 ± 12.5	7.9 ± 12.1
Median	2.0	5.0	4.0
[Min; Max]	[0; 55]	[0; 49]	[0; 55]
			Cont'd
No. of joint bleeds in the last 12 months			
n	25	26	51
Mean ± SD	2.4 ± 4.4	4.7 ± 7.5	3.6 ± 6.2
Median	0.0	1.5	0.0
[Min; Max]	[0; 15]	[0; 33]	[0; 33]
Target joints for bleeds [n (%)]			
No	20 (80.0)	17 (65.4)	37 (72.5)
Yes	5 (20.0)	9 (34.6)	14 (27.5)
Frequency of target joints [n (%)]			
0	20 (80.0)	17 (65.4)	37 (72.5)
1	5 (20.0)	4 (15.4)	9 (17.6)
2	0 (0.0)	3 (11.5)	3 (5.9)
3	0 (0.0)	1 (3.8)	1 (2.0)
4	0 (0.0)	1 (3.8)	1 (2.0)
Number of target joints			
n	25	26	51
Mean ± SD	0.2 ± 0.4	0.7 ± 1.1	0.4 ± 0.9
Median	0.0	0.0	0.0
[Min; Max]	[0; 1]	[0; 4]	[0; 4]

[a] Percentages based on the number of subjects with available data.
Source: Original from BLA 125574/0; Clinical Study Report A51496, V2.0, Table 8-4

6.3.10.1.3 Subject Disposition

A total of 58 subjects were enrolled in Part A of the study. As 7 of these subjects were screening failures, 51 PTPs (25 in the younger age group and 26 in the older age group) actually participated in Part A. All of these subjects completed the 6-month treatment period with Kovaltry.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

Twenty-three subjects (45.1%) out of 51 experienced a total of 53 bleeds within 48 hours after the previous prophylaxis injection. The median ABR was 0.00 bleeds/year with an interquartile range from 0.00 to 3.95 bleeds/year (mean: 2.04 ± 2.91 bleeds/year).

As shown in Table 35, the numbers of bleeds within 48 hours after the previous prophylaxis injection and the mean/median annualized ABRs were slightly lower in the older age group than in the younger age group.

Table 35. Number of total bleeds[a] within 48 h after the previous prophylaxis injection (ITT population)

	PTPs 0 – <6 years (N = 25)	PTPs 6 – 12 years (N = 26)	PTPs Total (N = 51)
No. of total bleeds within 48 h per year			
Mean ± SD	2.23 ± 2.77	1.86 ± 3.08	2.04 ± 2.91
Median	1.88	0.00	0.00
[Q1; Q3]	[0.00; 3.97]	[0.00; 1.96]	[0.00; 3.95]
No. of total bleeds within 48 h			
Mean ± SD	1.12 ± 1.39	0.96 ± 1.59	1.04 ± 1.48
Median	1.00	0.00	0.00
[Q1; Q3]	[0.00; 2.00]	[0.00; 1.00]	[0.00; 2.00]
Sum	28	25	53
No. of subjects with ≥1 bleed within 48 h			
No [n (%)]	12 (48.0)	16 (61.5)	28 (54.9)
Yes [n (%)]	13 (52.0)	10 (38.5)	23 (45.1)

a "Total bleeds" include spontaneous bleeds, trauma bleeds, untreated bleeds and injections with reason=other.
Bleeds within 48 h = bleeds within 48 hours of previous prophylaxis infusion
Q1 = 25% quartile; Q3 = 75% quartile.
Source: Original from BLA 125574/0; Clinical Study Report A51496, V2.0, Table 9-1

Approximately 60% (32/53) of bleeds that occurred within 48 h after a previous prophylaxis injection were trauma bleeds. The percentage of bleeds which were joint bleeds was approximately twice as high in the older group than in the younger age group (24.0% vs. 42.3%joint bleeds).

An overview of these data is shown in Table 36.

Table 36. Annualized number of bleeds within 48 h after the previous prophylaxis injection by bleeding type (ITT population)

	PTPs 0 – <6 years (N = 25)	PTPs 6 – 12 years (N = 26)	PTPs Total (N = 51)
No. of joint bleeds within 48 h per year			
Mean ± SD	0.47 ± 1.03	0.83 ± 1.68	0.65 ± 1.40
Median	0.00	0.00	0.00
[Q1; Q3]	[0.00; 0.00]	[0.00; 0.00]	[0.00; 0.00]
No. of joint bleeds within 48 h			
Mean ± SD	0.24 ± 0.52	0.42 ± 0.86	0.33 ± 0.71
Median	0.00	0.00	0.00
[Q1; Q3]	[0.00; 0.00]	[0.00; 0.00]	[0.00; 0.00]
Sum	6	11	17
No. of spontaneous bleeds within 48 h per year			
Mean ± SD	0.55 ± 1.46	0.16 ± 0.79	0.35 ± 1.17
Median	0.00	0.00	0.00
[Q1; Q3]	[0.00; 0.00]	[0.00; 0.00]	[0.00; 0.00]
No. of spontaneous bleeds within 48 h			
Mean ± SD	0.28 ± 0.74	0.08 ± 0.39	0.18 ± 0.59
Median	0.00	0.00	0.00
[Q1; Q3]	[0.00; 0.00]	[0.00; 0.00]	[0.00; 0.00]
Sum	7	2	9
No. of trauma bleeds within 48 h per year			
Mean ± SD	1.43 ± 2.41	1.04 ± 2.13	1.24 ± 2.26
Median	0.00	0.00	0.00
[Q1; Q3]	[0.00; 2.03]	[0.00; 1.90]	[0.00; 1.94]
No. of trauma bleeds within 48 h			
Mean ± SD	0.72 ± 1.21	0.54 ± 1.10	0.63 ± 1.15
Median	0.00	0.00	0.00
[Q1; Q3]	[0.00; 1.00]	[0.00; 1.00]	[0.00; 1.00]
Sum	18	14	32

Bleeds within 48 h = bleeds within 48 hours of previous prophylaxis infusion
Q1 = 25% quartile; Q3 = 75% quartile.
Source: Original from BLA 125574/0; Clinical Study Report A51496, V2.0, Table 9-2

6.3.11.2 Analyses of Secondary Endpoints

Annualized number of total bleeds during prophylaxis treatment

A total of 97 bleeds were reported, and the percentage of subjects who experienced at least 1 bleed was 54.9%. The mean (±SD) ABR of **total bleeds** was 3.75 ± 4.98 (median 1.90 bleeds/year with an interquartile range from 0.00 to 6.02). Both the percentage of subjects affected and the mean/ median ABRs were lower in the age group 6 to 12 years than in the age group 0 to <6 years.

Most of the bleeds reported were **trauma bleeds** (n = 59), resulting in a mean (±SD) ABR of 2.30 ± 3.98 trauma bleeds/year (median 0.00, interquartile range 0.00 to 3.87).

The mean (±SD) ABR of **spontaneous bleeds** was 0.63 ± 1.49 in the younger age group and 0.92 ± 2.61 in the older age group (median values: 0.00, interquartile range 0.00 to 0.00 for both age groups).

The mean (±SD) ABR of **joint bleeds** was 1.24 ± 2.74, and it was higher in the older age group than in the younger age group (0.79 ± 1.40 vs. 1.68 ± 3.57 joint bleeds/year).

An overview of these data is shown in Table 37.

Table 37. Summary of bleeds (ITT population)

	PTPs 0 – <6 years (N = 25)	PTPs 6 – 12 years (N = 26)	PTPs Total (N = 51)
No. of subjects with ≥ 1 bleed [n (%)]	15 (60.0)	13 (50.0)	28 (54.9)
No. of total bleeds [a] per year			
Mean ± SD	4.16 ± 5.02	3.37 ± 5.01	3.75 ± 4.98
Median	2.03	0.93	1.90
[Q1; Q3]	[0.00; 6.02]	[0.00; 5.77]	[0.00; 6.02]
No. of total bleeds [a]			
Mean ± SD	2.08 ± 2.50	1.73 ± 2.55	1.90 ± 2.51
Median	1.00	0.50	1.00
[Q1; Q3]	[0.00; 3.00]	[0.00; 3.00]	[0.00; 3.00]
Sum	52	45	97
No. of joint bleeds per year			
Mean ± SD	0.79 ± 1.40	1.68 ± 3.57	1.24 ± 2.74
Median	0.00	0.00	0.00
[Q1; Q3]	[0.00; 1.88]	[0.00; 2.05]	[0.00; 2.01]
No. of spontaneous bleeds per year			
Mean ± SD	0.63 ± 1.49	0.92 ± 2.61	0.78 ± 2.12
Median	0.00	0.00	0.00
[Q1; Q3]	[0.00; 0.00]	[0.00; 0.00]	[0.00; 0.00]
No. of trauma bleeds per year			
Mean ± SD	2.89 ± 4.06	1.72 ± 3.90	2.30 ± 3.98
Median	0.00	0.00	0.00
[Q1; Q3]	[0.00; 5.65]	[0.00; 1.93]	[0.00; 3.87]
No. of trauma bleeds			
Mean ± SD	1.44 ± 2.00	0.88 ± 1.99	1.16 ± 1.99
Median	0.00	0.00	0.00
[Q1; Q3]	[0.00; 3.00]	[0.00; 1.00]	[0.00; 2.00]
Sum	36	23	59

[a] Sum of spontaneous bleeds, trauma bleeds, untreated bleeds and injections with reason=other
Source: Adapted from BLA 125574/0; Clinical Study Report A51496, V2.0, Table 9-5

Hemostatic outcome of surgeries
See integrated overview of efficacy in section 7.2.

6.3.11.3 Subpopulation Analyses

Please see subgroup analyses by age in sections 6.3.11.1 and 6.3.11.2. For race, majority of the subjects are white (48/52) and all 3 non-white subjects didn't have any bleeds within 48 hours after prophylaxis treatment. The analysis results by region are displayed in Table 38. No substantial difference with regard to the primary endpoint was found.

Table 38. Annualized number of bleeds within 48 hrs after prophylaxis by region (ITT population)

			Previously Treated Patients (0-<6 years)	Previously Treated Patients (6-12 years)	Total
Region	North America	n	4	5	9
		Mean	4.11	0.80	2.27
		SD	4.33	1.10	3.27
		Median	3.21	0.00	1.86
		Min	0.0	0.0	0.0
		Max	10.0	2.1	10.0
	Europe	n	19	20	39
		Mean	1.96	1.71	1.83
		SD	2.45	2.90	2.65
		Median	0.00	0.00	0.00
		Min	0.0	0.0	0.0
		Max	6.0	8.1	8.1
	Israel	n	2	1	3
		Mean	1.02	10.09	4.04
		SD	1.44	.	5.33
		Median	1.02	10.09	2.04
		Min	0.0	10.1	0.0
		Max	2.0	10.1	10.1

Source: Adapted from BLA 125574/0; Clinical Study Report A51496, V2.0, Table 14.2/13

The results by frequency of prophylaxis treatment at start of study are summarized in Table 39. Subjects experienced more bleeds/year if they received prophylaxis treatment (at start of study) ≤2x/week (4.64 ± 5.83 bleeds/year) compared to subjects who were treated >2x/week (3.08 ± 4.21 bleeds/year). This difference was seen in both age groups.

Table 39. Annualized number of total bleeds[a] for selected subgroups (ITT population)

Stratification factor / subgroup		PTPs 0 – <6 years (N = 25)	PTPs 6 – 12 years (N = 26)	PTPs Total (N = 51)
Prophylaxis treatment regimen				
≤2x/week	n	9	12	21
	Mean ± SD	4.18 ± 5.54	3.89 ± 5.11	4.01 ± 5.16
	Median	0.00	1.88	1.86
	[Min; Max]	[0.0; 13.5]	[0.0; 14.1]	[0.0; 14.1]
>2x/week	n	16	14	30
	Mean ± SD	4.15 ± 4.89	2.92 ± 5.07	3.57 ± 4.93
	Median	2.95	0.00	1.97
	[Min; Max]	[0.0; 18.1]	[0.0; 17.7]	[0.0; 18.1]

[a] "Total bleeds" include spontaneous, trauma, untreated and injections with reason=other.
Source: Adapted from BLA 125574/0; Clinical Study Report A51496, V2.0, Table 9-13

6.3.11.5 Exploratory and Post Hoc Analyses

Description of bleed according to type, severity, and location

A total of 81 of 97 bleeds were treated and 72.8% of these bleeds were trauma bleeds. About half of the treated bleeds were skin/mucosa bleeds (46.4%), followed by joint bleeds (33.0%) and muscle bleeds (9.3%). Three bleeds were severe, others were either mild (51.5%) or moderate (45.4%) in intensity.

There were several differences in the characteristics of bleeds between the two age groups: When compared to the older age group, the percentage of trauma bleeds in

subjects in the younger age group was higher (81.8% vs. 62.2%), their percentage of skin/mucosa bleeds was higher (53.8% vs. 37.8%), and a higher percentage of their bleeds was mild in intensity (63.5% vs. 37.8%).

An overview of these data is shown in Table 40.

Table 40. Characteristics of treated bleeds (ITT 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)
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

N: the number of total bleeds

Source: Adapted from BLA 125574/0; Clinical Study Report A51496, V2.0, Table 9-6

Number of injections (for the treatment of bleeds) per bleed

A total of 134 injections of Kovaltry were administered for the treatment of the 81 bleeds (16 of the 97 bleeds were not treated).The median number of injections was 1 and ranged between 0 and 9 in both age groups. The majority of bleeds (89.7%) were treated with ≤2 injection.

A summary of the treatment of bleeds is shown in Table 41.

Table 41. Treatment of bleeds (ITT population)

	PTPs 0 – <6 years (N = 52)	PTPs 6 – 12 years (N = 45)	PTPs Total (N = 97)
Reason for first injection [n (%)]			
n	44	37	81
Spontaneous bleed -1st injection	8 (18.2)	12 (32.4)	20 (24.7)
Trauma bleed -1st injection	36 (81.8)	23 (62.2)	59 (72.8)
Other	0 (0.0)	2 (5.4)	2 (2.5)
No. of injections per bleed			
n	52	45	97
Mean ± SD	1.3 ± 1.8	1.4 ± 1.7	1.4 ± 1.7
Median	1.0	1.0	1.0
[Min; Max]	[0; 9]	[0; 8]	[0; 9]
Sum	70	64	134
No. of bleeds by number of injections [n (%)]			
n	52	45	97
Not treated	8 (15.4)	8 (17.8)	16 (16.5)
1 injection	37 (71.2)	28 (62.2)	65 (67.0)
2 injections	3 (5.8)	3 (6.7)	6 (6.2)
3 injections	1 (1.9)	2 (4.4)	3 (3.1)
>3 injections	3 (5.8)	4 (8.9)	7 (7.2)

Source: Adapted from BLA 125574/0; Clinical Study Report A51496, V2.0, Table 9-7

Subject's assessment of response to treatment of bleeds

The response to treatment of bleeds was done for the 81 treated bleeds. The response was assessed as "good" or "excellent" in 90.1% (95% CI: 81.5%, 95.6%) of the cases (97.8% in the younger age group and 81.0% in the older age group). In 1 of the 81 treated bleeds (1.2%) the response was assessed as "poor".

For a summary of these data, see Table 42.

Table 42. Response to treatment of bleeds (ITT population)

	PTPs 0 – <6 years (N = 52)	PTPs 6 – 12 years (N = 45)	PTPs Total (N = 97)
Response to treatment [n (%)]			
Missing	8	8	16
n	44 (100.0)	37 (100.0)	81 (100.0)
Excellent	20 (45.5)	12 (32.4)	32 (39.5)
Good	23 (52.3)	18 (48.6)	41 (50.6)
Moderate	0 (0.0)	7 (18.9)	7 (8.6)
Poor	1 (2.3)	0 (0.0)	1 (1.2)

Source: Original from BLA 125574/0; Clinical Study Report A51496, V2.0, Table 9-8

6.3.12 Safety Analyses

As of January 15, 2016, 20 PUPs have been included in the clinical study and 16 have been treated with Kovaltry. Three PUPs developed high titer inhibitors and 4 subjects (3 PUPs and 1 PTP) developed low titer inhibitors in the Leopold Kids study.

6.3.12.3 Deaths

No subjects died during the study.

6.3.12.4 Nonfatal Serious Adverse Events

Nine subjects (17.6%) experienced at least one SAE each during the study: five subjects prior to start of treatment (three in the younger age group and two in the older age group) and five subjects (all of them in the older age group) during the treatment period. One subject experienced one SAE before and one SAE during treatment.

None of the SAEs were rated as drug-related and all SAEs resolved by the end of the observation period. None of the SAEs led to discontinuation of study drug.

The core information for all SAEs is shown in Table 43. No subject developed inhibitors. Subject (b) (6) who experienced a gastrointestinal bleeding was diagnosed with Von Willebrand factor disease type 3 during the extension period.

Table 43. Listing of all SAEs during the study (safety population)

SID	Age (years)	Preferred term (MedDRA v. 15.1)	Severity	Treatment-emergent?	Drug-related?	Outcome
(b) (6)	4	Device malfunction	-	no	no	recovered/ resolved
	4	Central venous catheterisation	moderate	no	no	recovered/ resolved
	4	Haemarthrosis	mild	no	no	recovered/ resolved
	10	Mental status changes	mild	no	no	recovered/ resolved
	6	Haemarthrosis	mild	no	no	recovered/ resolved
		Bacterial infection	moderate	yes	no	recovered/ resolved
	11	Gastroenteritis	severe	yes	no	recovered/ resolved
	6	Tooth abscess	moderate	yes	no	recovered / resolved with sequelae
		Dental cleaning	mild	yes	no	recovered/ resolved
	7	Nervous system disorder	moderate	yes	no	recovered / resolved with sequelae
	10	Haemorrhagic anaemia	moderate	yes	no	recovered/ resolved
		Viral infection	moderate	yes	no	recovered/ resolved

Source: Original from BLA 125574/0; Clinical Study Report A51496, V2.0, Table 10-4

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Comparison of the CS/EP and CS/ADJ Potency Assignments

7.1.1 Methods of Integration

In an addendum to Leopold I report, the non-inferiority of the CS/EP potency assignment in comparison to the CS/ADJ potency assignment was to be demonstrated based on the comparison of ABRs during both potency periods in patients receiving Kovaltry for prophylaxis. For this purpose, 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.

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.

Considering the mentioned differences and appropriateness for the integrated analysis, 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.

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.

7.1.2 Statistical Considerations & Statistical Analysis Plan

Primary endpoint

The primary endpoint was the ABR for total bleeds. The differences in annualized bleeding rates within each subject (CS/ADJ versus CS/EP) were considered for all subjects having annualized bleeding rates for both potency periods.

Analysis populations

ITT population:	All subjects in the safety population who received prophylaxis treatment and have injection/bleeding data from the EPD.
PP population:	All ITT subjects who have no major protocol deviations and have EPD data from both cross-over periods.

For the non-inferiority testing, the PP population was to be used for the primary test, the ITT population was to be supportive.

Sample size determination

It was assumed subjects have an average of 5 bleeds per year on each potency (CS/EP and CS/ADJ). Subtracting these bleeding rates within each subject, a mean of 0 bleeds per year and a standard deviation of 6 bleeds per year (reference: data from Bayer study KG0201-EU) were expected. Using an one-sided 95% confidence interval, 80% power, an attrition rate of 15%, a sample size of 120 subjects was required using a non-inferiority margin of 1.5 bleeds per year.

Statistical methodology

The Hodges-Lehmann exact procedure using STATXACT in SAS version 8 or higher was to be used. All variables were to be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum were to be calculated for metric data. Frequency tables were to be generated for categorical data.

7.1.3 Disposition of subjects

Disposition of subjects for the primary and general efficacy analysis

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.

Table 44 displays the subject flow of all subjects treated on a prophylaxis schedule in Leopold I, Leopold II and both studies combined.

Table 44. Disposition of subjects for the primary and general efficacy analysis (ITT/safety population)

	Pooled N=121 n (%)	Leopold I N=62 n (%)	Leopold II N=59 n (%)
Number of subjects treated	121 (100.0)	62 (100.0)	59 (100.0)
Completed whole study [a]	108 (89.3)	49 (79.0)	59 (100.0)
Not completed whole study [a]	13 (10.7)	13 (21.0)	0 (0.0)
Primary reason:			
- Starting another study	8 (6.6)	8 (12.9)	0 (0.0)
- Withdrawal by subject	2 (1.7)	2 (3.2)	0 (0.0)
- Adverse event (AE)	1 (0.8)	1 (1.6)	0 (0.0)
- Non-compliance with study drug	1 (0.8)	1 (1.6)	0 (0.0)
- Physician decision	1 (0.8)	1 (1.6)	0 (0.0)
Subjects at start of 1st cross-over period	121 (100.0)	62 (100.0)	59 (100.0)
Completed 1st cross-over period	120 (99.2)	61 (98.4)	59 (100.0)
Terminated during 1st cross-over period	1 (0.8)	1 (1.6)	0 (0.0)
Primary reason:			
- Withdrawal by subject	1 (0.8)	1 (1.6)	0 (0.0)
Subjects at start of 2nd cross-over period	120 (100.0)	61 (100.0)	59 (100.0)
Completed 2nd cross-over period	120 (100.0)	61 (100.0)	59 (100.0)
Terminated during 2nd cross-over period	0 (0.0)	0 (0.0)	0 (0.0)
Subjects at start of extension [b]	-	55 (100.0)	-
Completed extension	-	43 (78.2)	-
Terminated during extension	-	12 (21.8)	-
Primary reason:			
- Starting another study	-	8 (14.5)	-
- Adverse event	-	1 (1.8)	-
- Non-compliance with study drug	-	1 (1.8)	-
- Physician decision	-	1 (1.8)	-
- Withdrawal by subject	-	1 (1.8)	-

[a] Including extension part of Leopold I for subjects who entered the extension.
[b] Applicable in Leopold I only.

Source: Original from BLA 125574/0; Clinical Study Report PH37290, V1.0, Table 8-1

Disposition of subjects for the analysis of efficacy during surgery

Forty subjects (18 in Leopold I part B and extension, 7 in Leopold I part C and 15 in Leopold II) underwent major and/or minor surgeries during the 2 studies. One further subject was enrolled in Leopold I part C, but did not actually undergo surgery (screening failure).

7.1.4 Analysis of Primary Endpoint

The 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. Analysis using the ITT population resulted in the same conclusion. Table 45 shows a summary of these analyses.

Table 45. Difference in annualized total bleeding rates between CS/ADJ and CS/EP dosing: Non-inferiority testing[a]

	PP population (N = 118)	ITT population (N = 121)
Median difference (Hodges-Lehmann estimate)	-0.012	0.011
Lower limit of the 1-sided 95% confidence interval	**-1.038**	-0.972
2-sided 95% confidence interval	[-1.232; 1.066]	[-1.089; 1.166]

Note: The primary result of the non-inferiority testing is the 1-sided 95% confidence interval for the difference in the PP population (printed in bold). Non-inferiority margin = -1.5 bleeds/year.

[a] Difference: Prophylaxis CS/ADJ minus prophylaxis CS/EP.

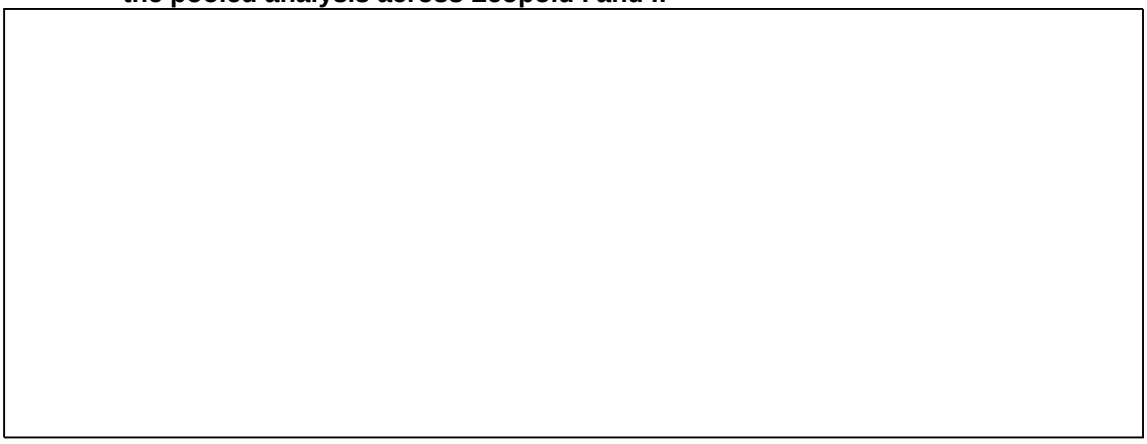
Source: Original from BLA 125574/0; Clinical Study Report PH37290, V1.0, Table 9-1

Reviewer's comment: The applicant didn't specify if the predefined margin of -1.5 is for the mean or the median in their submissions. They pre-specified they would use a Hodges-Lehmann estimator, which estimates the population median. However, when they determined the sample size, they used the paired t-test, which implies that the -1.5 margin should apply to the mean. I conducted a sensitivity analysis using the paired t-test with the PP population, and the conclusion remains the same. Using the PP population, the mean difference is -0.01 and the lower limit of the one-sided 95% CI is -0.801. The lower limit is greater than the predefined margin of -1.5bleeds/year, so the non-inferiority of CS/EP dosing versus CS/ADJ dosing was statistically met.

Supportive analysis

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 (Table 46). Non-inferiority of CS/EP-based vs CS/ADJ-based dosing in relation to prevention of bleeds during prophylaxis is unaffected.

Table 46. Bleeds per year, total population and excluding 9 prophylaxis subjects from the pooled analysis across Leopold I and II



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

7.2 Indication #2: Perioperative Management

For the efficacy analysis of surgeries, the data from surgeries in Leopold I (Part B, Part C and extension), Leopold II and Leopold Kids is considered.

Leopold I and Leopold II

Major surgeries

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 and exposed, or a substantial impairment of physical or physiological functions was produced (*e.g.*, laparotomy, thoracotomy, craniotomy, joint replacement, or limb amputation).

Twelve major surgeries for which Kovaltry was used for hemostatic control were performed during Leopold I (5 during the extension of Part B and 7 during Part C), and 1 during Leopold II. With one exception, all surgeries were elective.

Seven of the 13 major surgeries in total were orthopedic surgeries. The initial Kovaltry doses administered ranged between 3,000 and 5,000 IU.

The blood loss during and after surgery was within expected ranges, and the hemostatic control was assessed by the investigators/surgeons as good (76.9%) or excellent (23.1%) in all cases.

A summary of the main characteristics of major surgeries in Leopold I and Leopold II is given in Table 47.

Table 47. Listing of all major surgeries in Leopold I and Leopold II (surgery set)

Minor surgeries
Minorsurgery was defined as any surgical procedure (elective or emergent) that did not involve general anesthesia and/or respiratory assistance (*e.g.*, minor dental extractions, incision and drainage of abscess, or simple excisions).
Thirty-two subjects underwent a total of 46 minor surgeries (26 surgeries in 18 subjects during Leopold I and 20 surgeries in 14 subjects in Leopold II). Twenty-eight of the minor surgeries (60.9%) were dental surgeries. Eight (17.4%) of the minor surgeries were performed under general anesthesia, five (10.9%) of them were post-surgical wound care measures after compartment syndrome splitting in SID (b) (6) (see major surgery).
For three (6.5%) surgeries, no Kovaltry injections in addition to the regular prophylaxis injections were documented. The individual Kovaltry initial doses for all other minor surgeries ranged between 1500 IU and 5000 IU.

The hemostasis was assessed as excellent (53.5%) or good (46.5%) in all cases. No subjects required any blood transfusions.

Leopold Kids
One subject (SID (b) (6), 6 years) underwent a major surgery during the study. A tooth extraction was performed during dental cleaning. There was no blood loss reported during the surgery and no blood transfusions were necessary. The subject received two injections with a total dose of 2500 IU Kovaltry (108.7 IU/kg) on the day of surgery, 1000 IU in the morning (pre-surgery) and 1500 IU in the evening (after surgery). Hemostasis was assessed as “good”.

No minor surgeries, injections for minor surgeries or blood transfusions were reported in Part A of the study.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

I 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.

On-demand treatment and control of bleeding episodes
A total of 1892 bleeding episodes in 108 subjects were treated with Kovaltry in Leopold I and Leopold II studies. The majority of the bleeding episodes were spontaneous, localized in joints, and mild to moderate in severity. In Leopold I study part B and Leopold II study respectively, the treatment responses in a total of 1850 treated bleeds were assessed by the subjects compared to their previous treatment experience as: “good” or “excellent” in 80.9% and 68.2% of cases, “moderate” in 16.2% and 29.9% of cases, or “poor” in 3% and 1.9% of cases.

A total of 97 bleeding episodes in 28 pediatric subjects were treated with Kovaltry in Leopold Kids study. Majority (96.8%) of the bleeds were mild to moderate in severity. Fifty-nine (72.8%) bleeds were trauma related. During the 6 month treatment period, the median dose for the treatment of breakthrough bleeds was 36.94 IU/kg/injection (range 20.8–71.6 IU/kg). The hemostatic efficacy in on-demand

treatment of bleeds was assessed as either "good" or "excellent" in 90.1% of cases. The majority of bleeds (89.7%) were successfully treated with ≤2 injections.

Perioperative management of bleeding
A total of 14 major and 46 minor surgeries were performed in 44 previously treated subjects (43 adults and adolescents and 1 child under 12 years of age) with severe Hemophilia A. Seven of the 14 major surgeries were orthopedic procedures, including joint replacement. Approximately 51% of the minor surgeries were dental extractions. All subjects received Kovaltry as bolus injections. The blood loss, during and after surgery, was within expected ranges. Hemostatic control was assessed by surgeons as "good" or "excellent" for all cases.

Routine prophylaxis to reduce the frequency of bleeding episodes
Leopold I study demonstrated the efficacy and safety of routine prophylaxis with Kovaltry. Leopold II study demonstrated the superiority of prophylaxis over on-demand treatment with Kovaltry during a one-year treatment period. In both studies, the primary efficacy variable was the ABR of all bleeds which was analyzed in 62 subjects in Leopold I, 55 subjects in Leopold I Extension and 80 subjects in Leopold II (59 prophylaxis, 21 on-demand). In Leopold I, the prophylactic regimen was 20 to 50 IU/kg two or three times per week in which the dosing frequency was assigned by the investigator based on the patient's individual requirements. In Leopold II, the prophylactic regimen was 20 to 30 IU/kg two times per week or 30 to 40 IU/kg three times per week and the treatment group was assigned by randomization. The mean (SD) and median ABR for the ITT population in Leopold I were 3.8 (5.2) and 1.0 bleeds/year, respectively. In Leopold II, the mean (SD) and median ABR in subjects receiving on-demand therapy were 57.7 (24.6) and 60 versus 4.9 (6.8) and 2 in the subjects receiving prophylaxis, respectively. The comparison of the bleeding rates between subjects receiving on-demand therapy versus prophylaxis using ANOVA demonstrated a statistically significant difference ($p<0.0001$). Poisson regression also yielded similar results. The percent reduction of prophylaxis over on-demand arms in ABR was 91.6% (95% CI: 87.9%, 94.2%) which was statistically significantly higher than 50% reduction.

Leopold Kids study, a multi-center, open-label, uncontrolled study demonstrated the efficacy of prophylaxis with Kovaltry in PTPs age 0 to 12 years. The primary efficacy variable was the ABR within 48 hours after the previous prophylaxis injection, analyzed for a total of 51 subjects: 25 below 6 years and 26 between 6 to 12 years of age. Kovaltry was administered at frequencies of either 2 times per week, 3 times per week or every other day. The frequency as well as dose (20–50 IU/kg) was adapted to individual subject's need. The mean ABR within 48 hours after prophylactic injection was 2.04±2.91 (median: 0.00 bleeds/year [IQR: 0.00-3.95]). The mean ABR at any time during the prophylaxis treatment regimen was 3.75±4.98 (median: 1.90 bleeds/year [IQR: 0.00–6.02]). The majority (32/53) of bleeds that occurred within 48 hours after a previous prophylaxis injection were trauma related. Twenty-three (45.1%) subjects reported no bleeds during the six-month treatment prophylaxis period.

Non-inferiority Testing of CS/EP versus CS/ADJ Potency
Data from Leopold I Part B and Leopold II (prophylaxis group) were combined to test the non-inferiority of prophylactic treatment dosing determined by CS/EP versus CS/ADJ. The median ABRs in the PP population were 1.98 bleeds/year in both the CS/EP and CS/ADJ periods. 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. This lower limit of the CI is greater than the non-inferiority margin of -1.5 bleeds/year, thus showing statistical non-inferiority of CS/EP dosing versus CS/ADJ. Analysis using the ITT population resulted in the same conclusion.

10.2 Conclusions and Recommendations
Based on the results of the three clinical studies, Leopold I, Leopold II, and Leopold Kids Part A and Part B, adequate statistical evidence supports the proposed indications of: on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis treatment to reduce the frequency of bleeding episodes in adults and children with hemophilia A.