



Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

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Re: STN 125574\0

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Product: Kovaltry®

Subject: Biologics License Application

Sponsor: Bayer Healthcare LLC / 0008

Material reviewed: 125574/0; 125574/0.4; 125574/0.29; 125574/0.33; 125574/0.37

1. INTRODUCTION

On 16 December 2014, Bayer Healthcare LLC submitted an original Biologics License Application (BLA, 125574/0) to the Food and Drug Administration (FDA) for Kovaltry® – a full length recombinant Factor VIII product formulated with sucrose and synthesized in a modified baby hamster kidney (BHK) cell line.

The proposed clinical indications for use in both adults and children with hemophilia A include:

- Routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes
- Control and prevention of bleeding episodes and peri-operative management (surgical prophylaxis)
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults, adolescents and children
- (b) (4)

Kovaltry is a sterile, stable lyophilized powder supplied in single use glass vial containing 250, 500, 1000, 2000 and 3000 International Units (IU). Kovaltry is to be reconstituted with 2.5 mL sterile water for injection (sWFI) for 250 IU, 500 IU, and 1000 IU and with 5mL sWFI for 2000 IU and 3000 IU.

Bayer has produced two full length rFVIII products that are currently licensed: Kogenate®, and Kogenate FS®. Kogenate, first introduced in 1993, was formulated with human albumin as final product stabilizer;

its successor Kogenate FS, licensed in the US and Europe in 2000, is formulated with sucrose as final product stabilizer. Kogenate, Kogenate FS, and Kovaltry are all synthesized in a BHK cell line. Kovaltry's similarities with Kogenate FS include an identical FVIII amino acid sequence, same molecular formula, same proteolytic processing and similar post translational modification distribution (glycosylation and sulfation). However, Kovaltry is produced in a modified BHK cell line which includes the gene for human shock protein 70 (HSP70). Co-expression of HSP70 was shown to inhibit apoptosis thereby reducing the release of intracellular proteases that could damage the rFVIII molecules and as a chaperon molecule, increases the proper folding of the FVIII protein, reducing protein aggregation. Kovaltry is a 3rd generation product in which all animal- and all human- derived additives have been eliminated from the cell culture and purification processes and a viral filtration step has been added to improve viral clearance.

2. KNOWN SAFETY CONCERNS

- a) Transmission of pathogens.** The introduction of recombinant coagulation factor therapy in the late 1980s has drastically reduced the risk of transmission of human blood borne viruses (Hepatitis B, hepatitis C and human immunodeficiency virus (HIV)). Since then, improvement of protein purification techniques, viral inactivation steps and the avoidance of human or animal proteins at any stage in the manufacturing process have further minimized the risk of pathogen transmission.
- b) Inhibitor development.** The risk of inhibitor development remains a major safety concern for this class of product whether plasma-derived or recombinant. The etiology of the development of inhibitors to FVIII has not been fully elucidated. It is thought to result from a host alloimmune response to infusions of FVIII. Independent risk factors for the development of FVIII inhibitors include F8 gene mutation, ethnicity, family history of inhibitors and age at first infusion. While no clinical trial has been conducted to determine the product specific risk estimate for inhibitor development, various retrospective analyses have shown that the overall risk may be up to 5% in previously treated patients (PTPs) and as high as 35% in previously untreated patients (PUPs) with severe hemophilia A (1). More recent publications from Gouw et al in 2013 (2), Calvez et al in 2014 (3) and Collins et al in 2014 (4) comparing various brands of rFVIII suggested a trend towards an increased risk of inhibitors development in PUPs with severe hemophilia A after Kogenate FS when compared to Advate, a full length rFVIII manufactured by Baxter. The difference in post-translational modification capability from the cell line used in the manufacturing process (BHK for Kogenate FS and CHO for Advate) was proposed as a biologically plausible explanation for the suggested increased immunogenicity of Kogenate FS (5). These findings were concerning. The results and methodology of the studies were the objects of in-depth review at the FDA and follow-up discussions with regulatory agencies in Europe, (6) and Canada, the sponsor, Bayer, and the World Federation of Hemophilia (WFH) (6). These concerns led to the sponsor's agreement for a labeling change to include a summary of the findings to the "Post-marketing" section of the package insert in August 2015.
- c) Host cell proteins.** The presence of cell-culture-derived "process impurities" such as "Host Cell Proteins" (HCP) has been detected in final recombinant products, and so have antibodies to these non-human proteins in subjects treated with recombinant biologics. The clinical significance of the presence of these antibodies is unclear. The main concern is that immune response to the native host-cell proteins could have an effect on the immune response to the formulated product, resulting in reduced product safety and efficacy. In addition, cross-reactivity to human proteins could potentially lead to auto-immune conditions. Kovaltry is the first rFVIII product manufactured in a BHK cell line modified to include the gene to HSP70.

3. OBJECTIVES

The purpose of this memorandum is to review 1) the available safety data for Kovaltry submitted in the original BLA application and 2) the Pharmacovigilance Plan (PVP). A search of PubMed for published literature with safety related endpoints using the search terms "safety" and "Kovaltry" revealed no

additional documents to review. Materials reviewed as part of this comprehensive safety review are listed in Table 1 below.

Table 1. Materials Reviewed

Document Type	Document	Source
Summary of completed clinical studies	Leopold I , Leopold II, Leopold Kids Part A (PTPs)	Kovaltry, 125574/0
Partial Study Report	Leopold Kids <ul style="list-style-type: none"> Part B (PUPs) (ongoing) Optional Extension Phase (ongoing) 	Kovaltry , 125574/0
Risk Management Plan	Risk Management Plan – Version 1	Kovaltry, 125574/0
Clinical Study Report	Interim safety update of PUPs in Part B and extension subjects	Kovaltry, 125574/0.4
Response to Info request (Clinical) dated 24Aug2015 and 01Sep2015	Updated complete inhibitor data (PTPs and PUPs)	Kovaltry 125574/0.29
Literature References	WFH: Guidelines for the Management of Hemophilia 2nd Edition 2012	Kovaltry 125574/0.33
Other study reports/ Protocol Amendment	EUHASS* Protocol Version 4 PedNet** Protocol 5.1	Kovaltry 125574/0.37

*EUHASS: European Haemophilia Safety Surveillance System

**The European Paediatric Network for Haemophilia Management and the PedNet Haemophilia Registry

4. PHARMACOVIGILANCE PLAN REVIEW

4.1 Clinical Safety Database

Demonstration of the clinical safety of Kovaltry in PTPs is based on 3 clinical studies: Leopold I, Leopold II and Leopold Kids. Leopold Kids Part A was carried out in PTPs, Leopold Kids Part B in PUPs, and the Optional Extension Phase in PTPs and PUPs. Part B and Extension are ongoing at the time of this report; however, this memo includes a review of the safety updates for the Leopold Kids Part B and Optional Extension with data as of Aug 25, 2015 submitted by the sponsor on 2 September 2015 in Amendment 125574/0.29

Leopold I (protocol 12954) entitled “A two-part, randomized, cross-over, open label trial to evaluate the pharmacokinetics, efficacy and safety profile of plasma protein-free recombinant FVIII formulated with sucrose (BAY 81-8973) in previously treated subjects with severe hemophilia A under prophylaxis therapy” is a phase 1, and 2/3, multicenter, open-label, non-inferiority, partially controlled (pharmacokinetic part), cross-over clinical trial to assess safety and efficacy of Kovaltry (BAY 81-8973) in patients with severe hemophilia A. The study was conducted in North America, Europe, Israel, South Africa and Asia.

- **Part A** (phase 1) assessed the PK non-inferiority of Kovaltry as compared to Kogenate FS using bioequivalence criteria in PTPs via single dose (50IU/kg), intra-individual, cross-over trial design.
- **Part B** (phase 2/3) used an intra-individual, cross-over design to assess the safety, tolerability and efficacy of 1 year prophylaxis treatment, breakthrough bleeds and surgical procedures management with Kovaltry. Part B is considered the main part of the study.
- **Part C** investigated the hemostatic outcome of treatment with Kovaltry in additional patients undergoing major surgery.

Leopold I Extension was an optional 1 year extension phase offered to patients who completed one year of the study period in Part B for additional safety and efficacy.

Leopold II (Protocol 14319) entitled: “A phase II/III, randomized, cross-over, open-label trial to demonstrate superiority of prophylaxis over on-demand therapy in previously treated subjects with severe hemophilia A treated with plasma protein-free recombinant FVIII formulated with sucrose (BAY 81-8973)” aimed to demonstrate the superiority of prophylaxis treatment over on-demand therapy by a clinically significant decrease in bleeding rate during 12 month of treatment with Kovaltry. **This study was considered the pivotal study for the routine prophylaxis indication in adults in the US.** Leopold II was conducted in Europe, North and Middle America, South Africa and Asia.

Leopold Kids (Protocol 13400) entitled “A multi-center Phase III uncontrolled open-label trial to evaluate safety and efficacy of BAY 81-8973 in children with severe hemophilia A under prophylaxis therapy” is phase 2/3, randomized, cross-over trial to demonstrate the safety and efficacy of treatment with Kovaltry for prophylaxis, break through bleeds and surgery in children with severe hemophilia A. The study had three parts of which only Part A is completed.

- **Part A** (completed) investigated 51 PTPs, first treating PTPs between 6 and 12 years of age, followed by enrollment of PTPs <6 years old. Treatment duration was about 6 months and with at least 50 exposure days (EDs).
- **Part B** (ongoing) is to include at least 25 PUPs <6 years of age with 50 EDs each. This part began enrolment after 20 children in Part A had each accumulated 50 EDs.
- **Optional Extension Phase** (ongoing) for patient who completed Part A or B and wished to continue (until at least 100 EDs per patient are available or until market authorization).

Table 2. Study Subjects Enrolled in Pre-licensure Safety Studies of Kovaltry

Protocol number	Leopold I Part A 12954	Leopold I Part A, B, 12954	Leopold I Part C 12954	Leopold I Extension 12954	Leopold II 14319	Leopold Kids Part A 13400	Leopold Kids Part B* 13400	Leopold Kids Extension*
Study Type	PK trial (phase 1)	Part B main phase (phase 2/3)	Part C in surgical patients	Optional 1 year extension for those who completed Part A, B, C	Pivotal study for prophylaxis treatment in adults (phase 2/3)	Pediatric trial in PTPs <12 yo	Pediatric trial in PUPs <6 yo (ongoing)	PTPs and PUPs <12 yo who completed Leopold Kids Part A or B
Study Description	Comparison of PK Kovaltry vs Kogenate FS	Evaluation of safety & efficacy - adult & adolescent	Evaluation of safety & efficacy- adult & adolescent	Extension trial of safety & efficacy- adult & adolescent	Evaluation of safety and efficacy- adult & adolescent	Evaluation of safety and efficacy	Evaluation trial of safety & efficacy	Evaluation trial of safety & efficacy (for 100EDs)
Subjects (n) Total	28	62 (22 from Part A)	10	55	80	51	Target at least 25, 14 enrolled	
<18 yo	5	10			10	51	14	

PK = Pharmacokinetics. *Trial ongoing.

4.2 Pre-licensure Clinical Trial Safety Information

The summary for clinical safety is presented for the following data:

- Leopold I Part A
- Leopold I Safety Pool: across Part B and extension
- Leopold II Safety Pool across type of treatment (prophylaxis or on-demand)
- Leopold Kids Part A
- Leopold Kids Part B (interim analysis)

Patients who participated only in Part A and C of the Leopold I study are not included in any of the pools. In Part A, patients received only one dose of Kovaltry and Part C patients were treated during a major surgery and had an adverse event profile mainly determined by surgery itself.

4.2.1 Safety summary for Leopold I Part A

A total of 28 patients aged 12 to 61 years (median 28.5 years) were randomized (14 per sequencing group) of whom 5 were children, and received one dose of Kovaltry and Kogenate FS. Out of the 28 subjects, 7 developed at least one treatment emerging adverse event (TEAE) during treatment with either Kogenate FS or Kovaltry, none classified as serious. Three non-serious TEAEs in 2 patients were assessed as drug related (one patient experienced mild paresthesia during the Kogenate FS period and mild monocytosis in the Kovaltry period; another experienced mild monocytosis during the Kogenate FS period). Two non-treatment emergent SAEs were reported for a 37 year-old patient in the interval between the first and second PK session: hematuria and pneumonia.

4.2.2 Summary of Leopold I Safety Pool (across Part B and Extension)

Twenty-two out of the 28 patients who participated in Part A continued in Part B. A total of 63 patients were randomized into Leopold I Part B. One patient never started treatment. A total of 55 patients participated in the extension study. Patient's age ranged from 12 to 61 years with a median of 30.0 years. Ten were adolescent (12-17 years). Most were treated with prophylaxis before entry. The majority were White. In the year prior to the study, the mean number of bleeds was 11.5 ± 15.1 (median: 5; range: 0 to 55) and the mean number of joint bleeds was 8 ± 11.9 (median: 3.5; range: 0 to 55). Target joint for bleeds were present in 44 patients (71%). All but one patient out of the 62 accumulated at least 50 Exposure Days (EDs) to Kovaltry.

TEAEs: A total of 54 out of the 62 patients (87.1%) experienced at least one TEAE during the study. Most frequently reported TEAEs were under the Primary MedDRA dictionary System Organ Class (SOC) "*Infections and Infestations*" (n=33; 53.2%), including nasopharyngitis (n=14, 22.6%) and upper respiratory tract infections (n=14, 12.9%) and "*Gastrointestinal disorders*" (n=22, 35.5%).

Serious TEAEs: Ten subjects experienced at least one severe TEAE. These included acute myocardial infarction (n=1), chest pain (n=2), spinal pain, injury (n=1), ligament sprain (n=1), arthralgia (n=2), arthritis (n=2), compartment syndrome (n=1), joint range of motion decreased (n=2), epilepsy (n=1), loss of consciousness (n=1), anxiety (n=1), depression (n=1), somatoform disorder (n=1), and miscarriage of a partner (n=1). Except for one episode of chest pain reported during Part B by one subject, and during the 1-year extension by another subject, and one patient for whom suicidal ideation was reported twice during the 1-year extension of the Leopold I study, all SEAs were single occurrence. The acute myocardial infarction was assessed both as serious and drug related and led to the only discontinuation in the study. The event occurred in a 62 year old patient with several risk factors for cardiovascular events. The event occurred about a month after entering the extension period or 13 month after starting treatment and 4 hours after the last injection. The patient was treated with stent implantation and recovered.

Drug related events: Six out of 62 subjects experienced at least one drug related event. These events included acute myocardial infarction (n=1), nausea (n=1), injection site pain (n=1), seasonal allergy (n=1), myalgia (n=1), dysgeusia (n=1), headache (n=1), nasal congestion (n=1), rhinorrhea (n=1), pruritus (n=1), and flushing (n=1).

4.2.3 Leopold II Safety Pool

A total of 83 patients were randomized. Among them, 80 patients (on demand, n=21; low dose prophylaxis, n=28; high dose prophylaxis, n=31) received at least one injection of Kovaltry. Except for 1 patient in the on-demand group who was discontinued for non-compliance before the 2nd period, all other patients completed the 12-month study period. Mean age of the study population was 29.6 ± 11 years (median 28.5 years, range: 15 to 59 years) including 10 adolescents 15-17 years. All patients had received on demand treatment with FVIII and no regular prophylaxis for > 6 consecutive months in the previous 5 years as per protocol. The mean number of bleeds in the 12 months prior to the study period was 43.7 ± 26.8 (median 36, range 3 to 106) and about 2/3 were joint bleeds. Target joint bleeds were present in 72

patients (90%). All but 5 patients accumulated ≥ 50 EDs to Kovaltry. Median number of EDs in this study was 117.5. The 80 patients received a total of 9,881 injections of Kovaltry and the mean number of injections per patient was 123.51 ± 40.38 (median 123).

TEAEs occurred in 44 patients. Most frequently reported AEs were under the Primary MedDRA SOC “*Infections and Infestations*” including nasopharyngitis (16.3%) and upper respiratory tract infections (7.5%) or influenza (5%). Other SOC with $> 10\%$ of patients affected were “*Gastrointestinal disorders*” (13.8%) and “*Skin and subcutaneous tissue disorders*” (11.3%).

Serious TEAEs: There were 2 treatment-emergent SAEs, both rated as severe: asthma (n=1) and head injury (n=1). Neither was considered related to the study treatment. Neither patient died or was discontinued.

Drug related events: 3 patients experienced TEAEs assessed as drug related: 2 patients with skin related hypersensitivity reactions (infusion site pruritus and allergic dermatitis) and 1 patient who experienced mild transient lymphadenopathy immediately after the first injections.

4.2.4 Summary of Leopold I and II Safety Pool

A total of 142 patients received treatment in Leopold I (Part B and extension, (n=62)) or Leopold II (n=80) studies and were included in the Leopold I and II Safety Pool with a total of 25,890 EDs achieved. A total of 14 patients were discontinued before completion, including 12 who discontinued the optional extension, eight who started another study, two patients discontinued for non-compliance with study medication and withdraw consent and one patient discontinued because of an AE. A total of 25,890 EDs were achieved. The median number of days in the study was 371.5 days (range: 92.4 to 749.4 days) during which the patients accumulated a median of 159 EDs (range: 8-355 days). The majority of patients (n=125 or 88%) had achieved 100 EDs by the end of the studies. An additional 11 patients had 50-100 EDs. A total of 26,137 injections with Kovaltry were administered during the studies for either on-demand or prophylaxis treatment with a mean number of injections per patient of 183.33 ± 92.21 (median: 159.5; range: 8 to 424). The median age for the patient population of the Leopold I and II Safety Pool was 29 years (range: 12 to 61 years) including 20 adolescents between 12 and 17 years (10 from each study). The majority (n=101; 71.1 %) were White and 32 patients (22.5%) were Asian (all from Leopold II Study). The study duration was 2 years for the Leopold I study including the extension and 1 year for Leopold II study, and the FVIII consumption was higher in the Leopold I as compared to the Leopold II safety population.

TEAEs: Overall 98 (69%) of 142 patients experienced a TEAE. The incidence was higher in the Leopold I Safety Pool (87.1%) compared to the Leopold II Safety Pool (55%) most likely due to the fact that patients in the Leopold I safety pool which included the extension (1 year) were treated for twice as long (2 years) as those in the Leopold II study (1 year). Most TEAEs were mild or moderate. Drug related TEAEs occurred in less than 10% of the patients.

Serious TEAEs: There were 14 patients with treatment-emergent SAEs. Among these SAEs, one case of acute myocardial infarction (described above) was assessed as drug-related. This was the only AE which led to discontinuation from the study. All SAEs were either improved or resolved by the end of the study.

Drug related events: included skin related hypersensitivity reactions (n=2), mild transient lymphadenopathy (n=1), nausea (n=1), injection site pain (n=1), seasonal allergy (n=1), myalgia (n=1), dysgeusia (n=1), headache (n=1), nasal congestion (n=1), rhinorrhea (n=1), pruritus (n=1), flushing (n=1) and acute myocardial infarction (n=1).

4.2.5 Leopold II Kids Part A

All 51 children in the Leopold Kids Part A (25 PTPs < 6 years of age and 26 PTPs 6-11 years of age, White (94.1%)) completed the 6-month study period, accumulating a total of 3,618 EDs. The median number of days in the study was 182 days (range: 113 to 216 days) during which the patients accumulated a median of 73 EDs (range: 73-103) to Kovaltry. Only 1 patient had less than 50 EDs. A total of 3,669 injection of Kovaltry were administered during the 6-month study period (mean number of injections per patient was 71.9 ± 17.3 ; median: 77).

TEAEs: 35 out of 51 children (68.6%) experienced at least 1 TEAEs during the 6-month period. Most frequently reported events were in the following SOC: “*Infections and Infestations*” (51%), such as viral infections (9.8%) or nasopharyngitis (7.8%). Other SOC with more than 10% of patients affected were “*Gastrointestinal disorders*”, “*General disorders and administration site conditions*”, “*Respiratory, thoracic and mediastinal disorders*”, “*Injury, poisoning and procedural complications*”, and “*Nervous system disorders*”.

Serious TEAEs: There were 7 treatment-emergent SAEs in 5 patients which included anemia, gastroenteritis, bacterial infection, tooth abscess, dental cleaning, nervous system disorder, hemorrhagic anemia, viral infection. All were assessed as not drug related and all patients recovered. A 4 year old boy was discontinued because of a device related infection 6 month after the start of treatment with Kovaltry.

Drug related events: One event, pruritus, was reported as drug-related. Pruritus is a known skin-related hypersensitivity reaction for FVIII product.

4.2.6 Leopold Kids Part B (PUPs)

The 4-month Safety Update Report submitted on April 15, 2015 presents data related to Part B of Leopold Kids study (interim safety update in PUPs) with data as of December 31, 2014. A total of 16 PUPs subjects were enrolled in PART B of the Leopold Kids study, of whom 13 received the study drug. Of the thirteen PUPS patients who received the study drug, 3 were discontinued due to inhibitor development and had a premature withdrawal from the main study (Table 3). For these three patients the number of EDs was 6, 12 and 18 days. All 13 patients were male and White. One was less than 1 month old, 8 were between 1 month old and 1 year old, and 4 were between 1 and 6 years old. Among these 13 patients, 6 were treated on-demand and 7 were on prophylaxis. The median number of EDs was 25 days (mean: 30 days; range 2 to 55 days). Six patients had 20 EDs or less, 2 patients had between 20 and 50 EDs, and 5 patients had 50 EDs or more. No patient had 100 EDs or more.

Table 3. Subject disposition/all enrolled PUPs and extension subjects. Interim safety update of PUPs in Part B and extension subjects as of December 31, 2014

Disposition	PUPs n=16	Extension N=55
Number of subjects		
• Enrolled	16	55
• Screen failure	2	
• Study drug never administered	1	0
• Treated	13	55
• Ongoing	4	45
• Discontinued	3	2
• Other: Immune tolerance induction (ITI) therapy		1
• Pt dx with Von Willebrand disease		1
• Continued with extension	6	

Extension column includes all patients entering the extension, enrolled as PUPs or PTPs. ITI treatment is part of the extension period.

TEAEs: Twelve (92.3%) out of 13 PUPs reported at least 1 TEAE during the observation period (Table 4).

Table 4. Treatment emergent adverse events in PUPs as of December 31, 2014. Interim safety update of PUPs Part B.

Primary System Organ Class (MedDRA Version 17.1) • Preferred term	Leopold Kids, PUPs, Part B, Safety analysis set, N=13 (100%)
Number (%) of patients with at least one such event	12 (92.3%)
Ear and labyrinth disorders	1 (7.7%)
• Ear pain	1 (7.7%)
Gastrointestinal disorders	1 (7.7%)

• <i>Diarrhoea</i>	1 (7.7%)
• <i>Functional gastrointestinal disorder</i>	1 (7.7%)
General disorders and administration site conditions	4 (30.8%)
• <i>Facial pain</i>	1 (7.7%)
• <i>Pain</i>	1 (7.7%)
• <i>Pyrexia</i>	2 (15.4%)
Infections and infestations	8 (61.5%)
• <i>Bronchiolitis</i>	1 (7.7%)
• <i>Conjunctivitis</i>	1 (7.7%)
• <i>Ear infection</i>	1 (7.7%)
• <i>Gastroenteritis staphylococcal</i>	1 (7.7%)
• <i>Gastroenteritis viral</i>	1 (7.7%)
• <i>Influenza</i>	1 (7.7%)
• <i>Intertrigo candida</i>	1 (7.7%)
• <i>Rhinitis</i>	1 (7.7%)
• <i>Tracheitis</i>	1 (7.7%)
• <i>Upper respiratory tract infection</i>	1 (7.7%)
• <i>Varicella</i>	1 (7.7%)
• <i>Viral rash</i>	1 (7.7%)
Investigations	4 (30.8%)
• <i>Anti factor FVIII antibody positive</i>	4 (30.8%)
Musculoskeletal and connective tissue disorders	2 (15.4%)
• <i>Haemarthrosis</i>	1 (7.7%)
• <i>Soft tissue hemorrhage</i>	1 (7.7%)
Surgical and medical procedures	1 (7.7%)
• <i>Varicella immunization</i>	1 (7.7%)
Vascular disorders	1 (7.7%)
• <i>Haematoma</i>	1 (7.7%)

Serious TEAEs: Eight patients had a serious event including facial pain (n=1), bronchitis (n=1), gastroenteritis staphylococcal (n=1), anti FVIII antibody positive (n=4, 30.8%), medical observation (n=1), hemarthrosis (n=1), soft tissue hemorrhage (n=1), and hematoma (n=1). The study drug was withdrawn in one patient (a 9-month old boy) due to FVIII antibody development.

Drug related events: As noted in the PVP v1.0, and as of December 31, 2014 four patients, aged 11, 9, 8 and 4 months, developed FVIII inhibitors. A safety update provided by the sponsor on September 25, 2015 with data as of August 25, 2015 noted that 1 new subject had been enrolled and treated in the interval (Dec 31, 2014 to Aug, 25, 2015) and 2 additional subjects in the safety dataset had developed FVIII inhibitors. Thus as of August 25, 2015, 6/14 (42.8%) subjects had developed FVIII inhibitors, 3 high titers and 3 low titers. A description of each case is provided in the table below.

Table 5. PUPS with high and low titer inhibitors (Leopold Kids Part B, data as of August 25, 2015)

Subject ID (Age at study entry, race)	Risk factors	ED at inhibitor detection	Total ED at cut off	First positive FVIII inhibitor level (BU/ml)	Last measured inhibitor level (BU/ml)
Patient with high titer inhibitors (>5BU/ml)					
(b) (6) (9 months, White)	Intron 22 inversion (treatment start for major bleeds)	6	6	50	10
(b) (6) (1 year, White)	Small deletion, fever, infection	20 37	40	Positive * 14	5.9
(b) (6) (4 months, White)	Intron 22 inversion, family member with inhibitor	10	259	>45	135
Patient with low titer inhibitors (>0.6 BU/ml to ≤ 5BU/ml)					
(b) (6) (11 months,		10	372	0.6 (peak level 1.8)	negative

White)					
(b) (6) (8 months, White)		9	108	0.7 (peak level 2.4)	negative
(b) (6) (1 year, White)		43	102	2.4 (peak level 2.4)	negative

*Not in the database due to missing value, insufficient sample

Three PUPs (3/14=21.4%) developed high titer inhibitors, that required a change in treatment or management within the first 20 EDs. All three subjects were withdrawn from treatment and received ITI therapy.

The other 3 patients had low titer inhibitors that were transient and did not require change of treatment. None of these 3 subject required immune tolerance therapy or use of by-pass agent. The sponsor concluded that these low titers were not clinically relevant.

4.2.7 Summary of significant adverse events

There were no deaths during any of the studies.

Allergic reactions: There were no cases of anaphylactic reaction in any of the above studies. The presentation of hypersensitivity-related adverse events is based on MedDRA single PTs from the Standardized MedDRA queries “Angioedema”, “Anaphylactic reactions” and “Hypersensitivity reactions” together with the single PTs: tachycardia, sinus tachycardia, dizziness, nausea, vomiting, infusion site pruritus, chills and headache. A total of 29 patients (20.4%) in the Leopold I and II Safety Pool and 19 children (37.3%) in the Leopold Kids Part A reported at least one such event. Of these 7 patients experienced at least one drug-related TEAE, 6 patients with 7 events in the Leopold I and II Safety Pool (allergic dermatitis, flushing, headache, infusion site pruritus, nausea, pruritus, and seasonal allergy) and 1 patient in the Leopold Kids Part A (pruritus). All these events were classified as possibly related to hypersensitivity reactions. One case of asthma in a 33 year old patient from the Leopold II study was assessed as severe in intensity but not drug related.

Central venous access devices (CVAD) related events: 12 children between the ages of 2 to 10 years from the Leopold Kids Part A experienced CVAD related events. None assessed as treatment related. One significant TEAE although assessed as not drug-related was a case of device related infection in a 4 year-old boy 6 months after the start of treatment with Kovaltry leading to discontinuation of the study drug. The AE resolved in 3 days.

Cardiovascular events: A total of 7 patients (4.9%) in the Leopold I and II safety Pool reported at least one event in either SOC “*Cardiac disorders*” or “*Vascular disorders*”. Five patients reported hypertension and two patients reported palpitations or sinus tachycardia. Other events (bradycardia, tachycardia, acute myocardial infarction) were reported by 1 patient each. The most significant was the occurrence of acute myocardial infarction 4 hours after the last Kovaltry injection (and 13 month after start of treatment) in a 62 years old male with several risk factors for cardiovascular events. Causal relationship could not be excluded therefore the patient was discontinued. The patient recovered after 2 weeks with surgical stent implantation. For “*Vascular disorders*”, one case of flushing was classified as drug related.

Factor VIII inhibitor development: In the Leopold I, Leopold I extension, Leopold II and Leopold Kids Part A studies, no patient had a positive FVIII inhibitor level ≥ 0.6 BU/ml during the study duration. Data from the most recent interim safety update (August 24, 2015) for the ongoing Part B of the Leopold Kids study where only PUPs are enrolled, showed that 6 out of 14 PUPs (42.8%) developed inhibitors to FVIII (>0.6 BU/ml), among whom 3 (3/14 or 21.4%) had high titers (≥ 14 BU/ml) detected at 6, 10 and 37 EDs. All three were discontinued and all received immune tolerance induction (ITI) therapy. No change in treatment was required for the three patients with low titer inhibitors.

Anti-HSP70 antibodies: The sponsor noted that no specific pattern for changes regarding these antibodies was observed and none of the patients showed any specific clinical symptoms associated with the increases in the level of anti-HSP70 antibody. The majority of patients had detectable levels of anti-HSP70 at screening in the Leopold I and II studies and for the majority, these levels were below the cut-off value of 239ng/mL. A total of 13 patients in the Leopold I and II Safety Pool had values above the cut-off: 2 patients entered positive and became negative, 1 patient entered positive and remained positive, 5 patients entered negative and became transiently positive and 5 patients entered negative, became and remained positive.

In the Leopold Kids Part A, a 4 year old patient had a result above the cut-off at baseline prior to treatment which decreased below the threshold at the final visit.

Anti-BHK/HCP antibodies: 5 patients tested positive or possibly positive at baseline or during the studies. All of them entered the studies already positive: 2 patients in Leopold I were positive before and during most of the study but were negative at 12 month of the extension phase, 2 patients in the Leopold II study were possibly positive before the study and transiently negative at month 3 and 9, and one patient entered the Leopold II study as possibly positive but had only negative results during the study.

4.3 Proposed Pharmacovigilance Plan

The PVP submitted by the sponsor is summarized in Table 6 below.

The sponsor proposes the following post-marketing activities to address the important identified and potential safety concerns, including 1) Inhibitor developments in both PTPs and PUPs, 2) Allergic reactions, and 3) Cardiac events. The sponsor has developed 2 specific questionnaires to be completed by treating physicians as a follow-up to a reported event of inhibitor development or allergic reaction. The same questionnaires will be used to collect data from existing registries (EUHASS and PedNet). The objective of these questionnaires is to collect missing data elements and to characterize the patient and treatment-specific risk factors associated with either the development of inhibitors or allergic reactions.

Table 6. Safety concerns and planned pharmacovigilance actions.

SAFETY CONCERN	PLANNED ACTION(S)
Important Identified Risks	
1) Development of FVIII inhibitors 2) Hypersensitivity (skin associated and systemic hypersensitivity reactions to Kovaltry, including anaphylactic reactions)	<ul style="list-style-type: none"> ○ Routine pharmacovigilance and cumulative review in each PBRER ○ Enhanced data collection with targeted follow-up questionnaires to be used in spontaneous cases and in post marketing studies and clinical trials <ul style="list-style-type: none"> ▪ Registries/post-authorization safety studies in EUHASS and PedNet (study # 14149 and study # 15689) ▪ Clinical trials (Leopold Kids Part B, Leopold Kids extension and Leopold IV)
Important Potential Risks	
Cardiovascular risk	<ul style="list-style-type: none"> ○ Routine pharmacovigilance and cumulative review in each PBRER ○ Analyses of data from the existing EUHASS registries (post-authorization safety studies)
Ongoing Clinical Studies	
Leopold Kids Part B (study 13400)	<ul style="list-style-type: none"> ○ Objective: to investigate safety and efficacy in PUPs ○ Safety concerns: Development of inhibitors and hypersensitivity ○ Study start : Sep 2013 ○ Estimated study end: 2018 ○ Final study report: 2018
Leopold Kids extension (study 13400)	<ul style="list-style-type: none"> ○ Objective: to investigate safety and efficacy of long-term treatment with Kovaltry (at least 100 EDs) in PUPs and PTPs ○ Study start: Dec 2011 ○ Estimated study end: 2018

	<ul style="list-style-type: none"> ○ Final study report: 2018
Leopold IV (study 16817)	<ul style="list-style-type: none"> ○ Objective: to investigate safety and efficacy of Kovaltry in children from China – required for license in China ○ Safety concerns: Development of inhibitors and hypersensitivity ○ Currently under evaluation
Post-marketing safety studies	
Protocol 14149 Evaluation of cases with AEs of special interest in the EUHASS registry (epidemiological study)	<ul style="list-style-type: none"> ○ Safety concerns: development of inhibitors, hypersensitivity reactions and cardiovascular risk ○ Status: planned ○ Update to be provided with each PBRER
Protocol 15689 Evaluation of AEs of special interest in the PedNet registry (epidemiological study)	<ul style="list-style-type: none"> ○ Safety concern: Development of inhibitors ○ Status: Planned ○ Update to be provided with each PBRER

4.3.1 Review of the protocols of the Post-marketing safety studies

The EUHASS and the PedNet registries are existing established registries for all FVIII and FIX products. Analyses of the registry data are categorized as post-marketing epidemiological safety studies. These include Study 14149 and Study 15689.

Study 14149: The objective of this study is to evaluate adverse events of special interest in the EUHASS registry. The EUHASS registry is an investigator-driven registry funded by the EU, Bayer and other manufacturers of FVIII concentrate products. EUHASS is a prospective Hemophilia Safety Surveillance System opened to all European Hemophilia centers; currently 86 centers from 26 countries are taking part. Participating centers have agreed to report all relevant AEs in their patients (PTPs and PUPs) in a prospective manner for a period of 3 years. Events to be reported during the surveillance include allergic or other acute event, transfusion transmitted infections, inhibitors (antibodies against the coagulation factor), thrombosis, new cardiovascular events (heart attack or stroke), new malignancies, unexpected poor efficacy, other AEs possibly related to concentrate and death. The reporting of adverse events will be every 3 months. Participating centers will receive an e-mail every 3 months asking them if they had any of the reportable adverse events. If they report “yes”, they will be asked to report the adverse events. Additional information related to the event will be collected such as patient’s demographics, event diagnosis and date, lowest clotting factor level, and severity of bleeding disorder. This information will be obtained from standard patient management. No extra testing will be required.

At the end of each year, each participating center will provide data on their population exposed:

- # of patients with each diagnosis registered at the center during the previous 12 months,
- # of patients with each diagnosis with severe disease (<1% coagulation factor for hemophilia A or B, <10% for other factor deficiencies) who were registered at the center in the previous 12 months,
- # of patients with each diagnosis who received clotting factor concentrate in the previous 12 months,
- # of patients with each diagnosis who received bypassing agents for an inhibitor in the previous 12 months.

For each different clotting factor concentrate, centers will report:

- The total # of patients who received it in the previous 12 months,
- The total # of severe hemophilia A and B patients who received it in the previous 12 months,
- The # of severe hemophilia A and B patients who reached 50 lifetime exposures during the last 12 months; if more than one concentrate was used the patient must be counted against the last concentrate used and details of their exposure history must be given,
- The # of severe hemophilia A and B patients who reached 50 lifetime exposures more than 12 months ago and continued on the same concentrate throughout the previous 12 month period,

- The # of severe hemophilia A and B patients who reached 50 lifetime exposures more than 12 months ago and switched to this concentrate in the previous 12 month period.

The EUHASS registry working protocol version 4 states that EUHASS Steering Committee will produce 2 types of reports:

- Every 3 months: a report listing the adverse events reported to the study in the previous 3 months.
- Once a year: a more comprehensive report will include rates for the complications reported and a product-specific report based on the annual report.

The 3 month and annual reports will be sent to regulatory agencies in Europe and the US, to pharmaceutical companies funding the project and to each participating centers. Product-specific reports however will be sent only to the manufacturer of the individual product.

The enrollment of the first patient treated with Kovaltry is expected after product licensure. An update on patients receiving Kovaltry will be provided with each PBRER.

Study 15689: The objective of this study is to collect data on bleeding during neonatal period, endogenous (genetic) and exogenous (treatment related) determinants of inhibitor development, and long term outcome. The PedNet registry is an investigator-initiated registry of PUPs supported by Bayer Health Care Pharmaceuticals. It is a multicenter, observational cohort study of a population base of children with mild, moderate and severe hemophilia A or B born between January 1, 2000 through January 1, 2020, who have been treated in one of the participating Hemophilia Treatment Centers (HTCs). Well defined clinical data will be collected from the enrolled patient's medical files. Participating in the registry will not change the number of visits and all outcome parameters will be collected as part of routine care. Only patients diagnosed with hemophilia A or B, with FVIII activity <1 to 25%, and with complete data (record of factor treatment and bleeds) from start of treatment will be enrolled. Patients referred to a participating center because of inhibitor development, which may lead to selection bias, will not be eligible for the study. Subjects will be followed until 2020. Determinants include baseline FVIII/IX levels, family history, family history of inhibitors, FVIII/IX gene mutation, details on replacement therapy (according to each infusion for the first 50 EDs and annually thereafter), measurement of inhibitory antibodies, and surgery. Main outcome is the development of inhibitory antibodies defined by 2 positive inhibitor titers in combination with one recovery test showing a recovery of <66% of expected. All centers will perform testing inhibitors at least every 5 EDs during the first 20 EDs and thereafter every 3 months until 50EDs are reached. All participating laboratories use the Nijmegen modification of the Bethesda assay with local cut off values varying between 0.3 and <0.6 BU/ml. Local investigators will notify the principal investigator of all SAE, AE and AR, i.e. inhibitors, allergic responses and death, in a prospective manner for a period of 3 years. As the follow up in the registry is continuing for years and inclusion is ongoing, not all patients will have the same follow up (FU) in the database. To account for differences in FU and changes in inhibitor risk in relation with the number of exposure days, multivariate Cox regression analysis or conditional logistic regression will be used. The enrollment of the first patient treated with Kovaltry is expected after product licensure. An update on patients receiving Kovaltry will be provided with each PBRER.

The main differences between the 2 registries (Study 14149 and Study 15689) are the study populations and study design. EUHASS is a voluntary adverse event (AE) reporting system for Europe opened to all European hemophilia centers. As of April 29, 2015, 86 centers treating both children and adults (PUPs and PTPs) from 26 countries are participating. The PedNet registry is an international (Europe, Canada and Israel), multicenter, observational cohort database collecting data on children (PUPs and PTPs) with mild, moderate or severe hemophilia A and B born from January 1, 2000 until January 1, 2020 who are or have been treated in one of the participating hemophilia treatment centers (HTCs). Eligibility criteria for enrolment in the registry apply, most importantly a complete record of replacement therapy since initiation. Neither registry is designed for the sole purpose of specifically evaluating the post-marketing safety of Kovaltry.

Reviewer's note: Both registries present limitations, to include voluntary reporting of adverse events, lack of randomization to treatment leading to selection bias, center differences in the choice of treatment, and no central laboratory testing leading to misclassification bias.

5. INTEGRATED RISK ASSESSMENT

The available data submitted by the sponsor in support of this BLA have evaluated the known safety concerns for rFVIII products – infectivity, hypersensitivity, and immunogenicity. As a 3rd generation recombinant FVIII product, Kovaltry carries minimal risk of transmission of infectious agents such as Hepatitis viruses or HIV. In the clinical safety database, no subjects experienced drug related symptoms of infections.

Allergic and hypersensitivity reactions may occur with Kovaltry as with other rFVIII products. In the safety clinical database, 7 patients experienced at least one drug related hypersensitivity-related AE, 6 patients with 7 events in the Leopold I and II Safety Pool (allergic dermatitis, flushing, headache, infusion site pruritus, nausea, pruritus, and seasonal allergy) and 1 patient in the Leopold Kids Part A (pruritus). This OBE reviewer agrees with the sponsor's proposal to evaluate these types of reactions using a specifically designed questionnaire both for spontaneous reported events, in post-marketing registry studies in PedNet and EUHASS (study 14149 and study 15689, respectively), and in clinical trials (Leopold Kids Part B, Leopold Kids extension and Leopold IV).

Observational studies have shown that patients with hemophilia, including hemophilia A, with a lifelong hypercoagulability may have a lower cardiovascular mortality but have the same high prevalence of atherosclerotic plaques as the general population (7). The risk of developing cardiovascular events may be the same for individuals with cardiovascular risk factors whether these individuals are hemophiliacs or not. The safety database includes a case of acute myocardial infarction that occurred in a 62 year old male with several cardiovascular risk factors 4 hours after Kovaltry injection, leading to discontinuation and treatment with stent implantation. This OBE reviewer agrees with the sponsor's proposal to address the patient and treatment-specific risk factors associated with cardiovascular events through routine pharmacovigilance and the use of the EUHASS registry.

The risk of developing inhibitors to FVIII in hemophilia A patients is a well-known complication of FVIII replacement therapy. The lifetime risk of developing inhibitors in severe hemophilia patients is in the range of 20-30% and approximately 5-10% in moderate or mild disease (8). Inhibitor development occurs preferentially in PUPs and in patients with risk factors. In some cases the level of antibodies to FVIII is minimal and does not require any therapeutic intervention. In others however, the level of inhibitors is high enough to lead to complications such as severe bleeding that require evasion therapy. None of the 142 PTPs in the Leopold I and II Safety Pool developed inhibitors. Although these results are reassuring, the number of treated patients is quite small (n=142). More concerning is the fact that 6 out of 14 PUPs (42.8%) from the ongoing Leopold Kids Part B study developed inhibitors to Kovaltry. At the time of its last update (Aug 25, 2015), the Leopold Kids Part B study has enrolled slightly more than half of its target population (14 out of 25), yet the rate of inhibitor development is in the higher range of the expected rate in PUPs (40%).

Results of recent epidemiologic studies suggested a difference in risk of inhibitor development in PUPs following Kogenate FS when compared to Advate. This concern led the sponsor to agree to a labeling change. Speculation on the biological plausibility of a causal association between the risk of inhibitor development and Kogenate FS pointed to the post-translational modifications unique to the BHK cell lines on which Kogenate FS is produced. Kovaltry is also produced in a BHK cell line although modified to include the gene for human shock protein 70 (HSP70). The risk of inhibitor development in PUPs after Kovaltry appears to be in the higher range of expected values in the planned study population (6/14=42.8%). These results are concerning and warrant discussion on whether approval should be granted for the PUPs indication prior to the completion of the PUPs study.

The sponsor proposed to complete the Leopold Kids Part B after licensure and to further evaluate the development of inhibitor in PUPs using the post-marketing PedNet registry. This registry is a valuable

source of information for post-marketing safety studies. However it has significant limitations. These limitations include the potential for selection or information biases, and the lack of randomization to product administration (6). Therefore this OBE reviewer recommends that OBRR consider delaying a decision on the approval of Kovaltry in PUPs until the Leopold Kids Part B is completed. This provides a better risk estimate of inhibitor development in PUPs after Kovaltry. Including the results of the interim analysis of the PUPs study in the package insert at the expected time of licensure (providing the study has not been completed) may be an acceptable alternative. Final results of the PUPs should be included in the product label when the study is completed.

Antibody formation to HSP70 and BHK/HCP was evaluated because these proteins are expressed by the cell line. HSP70 serves as a chaperone molecule that increases the proper folding of the FVIII protein, potentially reducing protein aggregation. Kovaltry is the first rFVIII product manufactured in a BHK cell line modified to include the gene to HSP70. The main concern is that immune response to the native host-cell proteins could have an effect on the immune response to the formulated product, subsequently reducing its safety and efficacy. In addition, cross-reactivity to human proteins could potentially lead to auto-immune conditions. Sero-conversions by study subjects from positive to negative, and vice versa, for both anti-BHK/HCP antibodies and anti-HSP70 antibodies have been documented in the clinical safety database with no clear or consistent pattern of sero-conversion related to exposure to the study drug or associated clinical symptoms. Therefore the clinical significance of these antibodies remains unclear.

6. RECOMMENDATIONS

This OBE reviewer agrees with routine pharmacovigilance as proposed by the sponsor in the PVP, with adverse event reporting as required under 21 CFR 600.80. Periodic adverse event reports should include details of the potential risks and missing information identified in this safety review. The reviewed safety data do not substantiate a need for a post-marketing requirement (PMR) study or a Risk Evaluation and Mitigation Strategy (REMS).

In summary, OBE/DE recommends the following post-marketing safety surveillance activities:

1. Routine surveillance in accordance with 21 CFR 600.80
2. Enhanced data collection with targeted follow-up questionnaires to be used in spontaneous cases and in post marketing studies and clinical trials for inhibitor development and hypersensitivity reactions
3. Product-specific updates for Kovaltry from the two following existing safety surveillance registries for hemophilia (including the annual product-specific report from the EUHASS Steering committee) should be submitted with each PBRER:
 - a. Registry in PedNet (study 15689)
 - b. Registry in EUHASS (study 14149)
4. Consider delaying the Kovaltry approval for the indication of use in the subgroup of previously unexposed patients (PUPs) until a completed Leopold Kids Part B study provides additional inhibitor development information, or as an alternative include the results of the interim analysis of the PUPs study in the package insert at the expected time of licensure. Final results of the PUPs study should be included in the product label when the study is completed.

7. REFERENCES

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