U.S. FOOD & DRUG ADMINISTRATION

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Division of Epidemiology (DE)

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

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Subject:	Review of Pharmacovigilance Plan
Sponsor:	Bayer HealthCare LLC
Product:	JIVI® or damoctocog alfa pegol (BAY 94-9027): Recombinant B-domain deleted human coagulation factor VIII site-specifically conjugated with a 60 kDa branched polyethylene glycol (PEG) molecule.
Application Type/Number:	BLA/STN 125661/0.0
Proposed Indication:	On-demand treatment and control of bleeding episodes, perioperative management of bleeding, and/or routine prophylaxis to reduce frequency of bleeding episodes among previously treated adults and adolescents (12 years of age and older) with hemophilia A (congenital Factor VIII deficiency).
Submission Date:	August 30, 2017
Action Due Date:	August 30, 2018

1 Objective

The purpose of this memorandum is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) based on the safety profile of JIVI® (BAY 94-9027) and determine whether any post-marketing requirements are indicated.

2 Background

Hemophilia A is an X-linked recessive disease characterized by deficiency of coagulation Factor VIII (FVIII) that results in bleeding complications. Bleeding tends to occur in joints (most common site of bleeding, with recurrent bleeds resulting in hemophilic arthropathy), muscles, oropharynx, gastrointestinal tract, genitourinary tract, and rarely, brain. Severity of disease is defined according to the patient's FVIII level and is an important predictor of clinical manifestations.

Hemophilia A affects approximately 1/5000 live male births. While female carriers (heterozygotes) are expected to have 50% of normal FVIII activity (which is sufficient to prevent bleeding), some heterozygotes have symptoms similar to males with mild hemophilia (>5% endogenous FVIII). Management of hemophilia A involves measures to prevent bleeding in order to avoid long-term complications, pre-emptive treatment prior to and subsequent to invasive procedures/surgery to prevent/control bleeding, and treatment of bleeding episodes.

Several Factor VIII products are available for treatment of hemophilia A, and known risks involving this class of products include:

- *FVIII inhibitors*: Antibodies (usually IgG) directed against FVIII that occur in response to exogenous FVIII products, seen most frequently among individuals with severe disease (<1% endogenous FVIII activity) and early in treatment initiation. Because these inhibitors interfere with FVIII activity, bleeding can ensue despite treatment. Inhibitor formation is also influenced by other factors, including family history of inhibitors, gene mutations/polymorphisms, treatment intensity, race, and age.

- *Allergic-type hypersensitivity reactions*: These reactions may occur in response to foreign cell proteins or other components of FVIII products.

- *Transmission of pathogens*: related to factor therapy derived from human plasma or containing human proteins. The incidence of infection has markedly decreased since the introduction of screening for human immunodeficiency virus and hepatitis B/C, product purification methods, and recombinant FVIII products.

- *Catheter-related complications*: due to the need for chronic infusions, a central venous catheters (CVC) is often placed to facilitate intravenous access. Potential CVC complications include bleeding, thrombosis, and infection.

3 Product Information

3.1 Product description

JIVI®, damoctocog alpha pegol (BAY 94-9027) is a pegylated (60 kDa), B-domain deleted (BDD), recombinant (r) coagulation FVIII conjugated protein. Prior to conjugation, the active protein is a rBDD human coagulation FVIII produced by recombinant DNA technology in baby hamster kidney (BHK) cells. Site-specific conjugation of the variant BDD-rFVIII occurs at the cysteine amino acid position 1804 (within the A3 domain – to provide a consistent coagulation activity and high pegylation efficiency) with a single maleimide-derivatized 60 kDa branched PEG (two 30 kDa PEG) moiety. There is no addition of any human- or animal-derived protein in the cell culture, purification, or pegylation processes and final formulation.

The rFVIII protein of BAY 94-9027 is not metabolized by liver enzymes, and hepatic impairment is not expected to affect pharmacokinetics of the product. In addition, renal excretion is not expected. Based on this information pharmacokinetic studies were not conducted in patients with hepatic or renal impairment.

3.2 Proposed dosing regimen(s) and formulation

BAY 94-9027[a] is available as a sterile, nonpyrogenic, preservative-free, lyophilized powder supplied in single-use glass vials of varying strengths (b) (4), 500, 1,000, 2,000, and 3,000 international units (IU)) for reconstitution with water (diluent) at the time of use for intravenous administration. The product is provided in a package that also includes a container closure system and a prefilled diluent syringe.

Dosage IU/dL (or % of normal) depends on the indication, severity of Factor VIII deficiency, location and extent of bleeding, and the patient's clinical condition and response to therapy. The proposed dosing schedule is as follows:

<u>On-demand treatment and control of bleeding episodes</u>

Minor bleeding: 20-40 IU/dL; repeat every 24-48 hours until bleeding resolved.
Moderate bleeding: 30-60 IU/dL; repeat every 24-48 hours until bleeding resolved.
Major bleeding: 60-100 IU/dL; repeat every 8-24 hours until bleeding resolved.

<u>Perioperative management of bleeding</u>

Minor surgery: 30-60 IU/dL, pre- and post-operative; repeat every 24 hours for at least one day until healing is achieved.
Major surgery: 80-100 IU/dL, pre- and post-operative; repeat every 12-24 hours until adequate wound healing is complete, then continue therapy for at least another 7 days to maintain FVIII activity of 30-60% IU/dL.

<u>Routine prophylaxis</u>

The recommended regimen is (b) (4) IU/kg every (b) (days. Based on the patient's clinical characteristics, the regimen (b) (4) IU/dL every (b) (days (b) (4) 30-40 IU/dL two times per week.

The total recommended maximum dose per infusion is approximately 6,000 IU (rounded to vial size).

[a] The potency is determined with a chromogenic substrate assay, and one IU is defined by the current World Health Organization international standard for FVIII concentrate.

4 Materials Reviewed

Table 1. Materials reviewed in support of this assessment (BLA 125661)

Submit Date	Document Type	Document(s) Reviewed Source: Bayer
8/30/2017	Sequence 0001	Modules: 1.14.1.2 Annotated draft labeling text 1.16 Risk management plan 2.5 Clinical overview 2.7.4 Summary of clinical safety 5.3.5.2 Study reports of uncontrolled clinical studies 5.3.5.3 Integrated summary of safety
11/17/2017	Sequence 0008	Module 1.2 Cover Letters
3/9/2018	Sequence 0022	Module 1.2 (response to FDA Information Request #17 regarding post-marketing questionnaires included with PVP)
3/23/2018	Sequence 0027	Module 1.2 (EUHASS protocol, version 9, Feb 2018)
4/24/2018	Sequence 0036	Module 4 Nonclinical Study Reports
5/23/2018	Sequence 0041	Module 1.2 Cover Letters (response to FDA Information Request #30)
7/25/2018	Sequence 0051	Modules 1.2 Cover Letters and 1.16 Risk Management Plan

5 Summary of Prior Marketed Experience

Not applicable. Product does not have a history of regulatory approval and general use anywhere in the world.

6 Key Regulatory Events Relevant to PVP

- May 2014: European Medicines Agency (EMA) Scientific Advice – post-marketing surveillance study requirement in the event that 200 subjects with 100 exposure days (EDs) have not been followed in phase 2/3 and pediatric studies (the post-marketing surveillance study will include the number of patients needed to achieve the goal of 200 patients followed for 100 EDs).

- February 2017: EMA Scientific Advice – The outcome of this regulatory milestone was “agreement that due to the risk of developing both FVIII inhibitors and anti-PEG antibodies, hence the risk for loss of efficacy and/or hypersensitivity, initiation of a previously untreated patient (PUP) study is not acceptable. […] Proposed new age cut-off (patients $\geq$12 years) could avoid complications for younger patients, but patients and healthcare providers are not used to FVIII with an age limit. Risk for

off-label use to be addressed in the Risk Management Plan." Recommendations to address concern of PEG accumulation after long-term treatment and potential impact on tissues and organs (e.g., choroid plexus, kidney) within the frame of a post-authorization safety study and/or registries and to use biomarkers whenever applicable."

- May 31, 2017: FDA requested the sponsor to undertake a chronic (long-term) toxicity study (26 weeks) in immunodeficient male rats to identify potential safety concerns for humans and potential long-term adverse events that may need monitoring in the PVP.

7 Brief Overview of Studies, Select Definitions, and Notable Findings

7.1 Completed studies

In all studies, study participants were males with severe Hemophilia A (Table 2).

Table 2. Overview of clinical trials of BAY 94-9027*

Study Feature	**Phase 1**	**PROTECT VIII**	**PROTECT KIDs (Main study)**
Phase	Phase 1	Phase 2/3	Phase 3
Site(s)	4 centers in the United States (U.S.)	60 centers in 20 countries across Europe, North America, South America, and Asia	37 centers in 17 countries in Europe, North America, South America, Asia (Israel), and Oceania (New Zealand)
Type of endpoint	PK and safety	Efficacy and safety Long-term safety over ≥100 EDs	PK, efficacy, and safety
Number of subjects: treated/ completed	14/14	Main Study Part A On demand: 20/18 Prophylaxis: 114/108 Part B 16/14 Extension Study Part A: 121/37 (78 ongoing) Part B: 19/16 (1 ongoing)	<6 years: 32/ 25 6-<12 years: 29/ 28 (61/53)
Age (years)	18-65 years	12-65 years	<12 years
Required number of EDs for study entry	≥150 EDs	≥150 EDs	>50 EDs

Study Feature	Phase 1	PROTECT VIII	PROTECT KIDs (Main study)
Select study criteria	No other bleeding disorder Inhibitor NEG (≤6 BU/ml) Immunocompetent (CD4+ >400/mm^3) AST or ALT ≤2x ULN T. bili <1.5x ULN Cr ≤1.5x ULN	No other bleeding disorder Inhibitor NEG (≤6 BU/ml) Immunocompetent (CD4+ >200/mm^3 if HIV+) AST or ALT ≤5x ULN Cr ≤2x ULN	No other bleeding disorder Inhibitor NEG (<6 BU/ml) No chemotherapy, immune modulatory drugs (other than anti-retrovirals), or chronic corticosteroids (>14 days) within past 3 months AST or ALT ≤5x ULN Cr ≤2x ULN

*Note: Table is based on information from the following sources: Section 2.7.6 Synopses of Individual Studies and Section 5.3.5 Reports of Efficacy and Safety Studies (select inclusion and exclusion criteria for each study). Abbreviations: BU, Bethesda units; Cr, creatinine; ED, exposures days; HIV, human immunodeficiency virus; NEG, negative; PK, pharmacokinetics; ULN, upper limit of normal range.

1. **Phase I Study** – multicenter, non-randomized, open-label study to evaluate pharmacokinetics (PK) and safety profile of BAY 94-9027 among previously treated patients (PTPs) with at least 150 exposure days (EDs) with other FVIII products prior to study entry who were 18-65 years of age with severe hemophilia A (<1% FVIII). All participants were male. The study was conducted at four centers in the U.S. In total, 14 patients were enrolled in this Phase I study. The study duration was 8 weeks.

2. **PROTECT VIII** – phase 2/3, multicenter, open-label, partially randomized study to demonstrate efficacy and safety of BAY 94-0927 for prophylaxis, treatment of bleeds, and surgery among PTPs with at least 150 EDs with other FVIII products prior to study entry who were 12-65 years of age with severe hemophilia A (<1% FVIII). The study was conducted at 60 centers in 20 countries across Europe, North America, South America, and Asia. The study includes three parts - Parts A and B (together considered the Main study) and an optional extension study:

    a. **Part A**: assessed PK, efficacy, and safety for prophylaxis and on-demand treatment of bleeding. Patients selected their preferred treatment arm (prophylaxis or on-demand) with the dose determined by the treating provider. All patients in Part A were followed for 36 weeks.

    b. **Part B**: assessed PK, efficacy, and safety in hemostasis during major surgery. This part of the study was open to those who participated in Part A.

    c. **Extension (optional)**: assessed efficacy and safety; participation was offered to individuals who had completed Part A so as to accumulate at least 100 EDs or until marketing of the drug.

In total, 134 patients were enrolled in PROTECT VIII studies. An overview of select inclusion/exclusion criteria in this study is detailed in Table 2.

3. **PROTECT KIDs** - phase 3, multicenter, open label, uncontrolled study to assess PK, efficacy, and safety of treatment with BAY 94-0927 for prophylaxis and treatment of bleeds in PTPs, <12 years of age, with at least 50 EDs with other FVIII products prior to study entry and severe hemophilia A (<1% FVIII). The study includes 3 parts – **Main** study (treatment duration was at least 50 EDs and a minimum of 6 months), **Part 2** (extension group; treatment duration 12 weeks), and **optional extension** study (offered to all participants of the main study and Part 2; treatment duration at least 50 additional EDs [minimum total 100 EDs] or until marketing). The PROTECT KIDs studies were conducted at 37 centers in 17 countries in Europe, North America, South America, Asia (Israel), and Oceania (New Zealand).

7.2 Ongoing studies

7.2.1. PROTECT VIII ongoing extension

Patients who completed Part A of PROTECT VIII study were offered participation in this extension for collection of additional efficacy and safety data and for receipt of at least 100 EDs of BAY 94-9027 or until marketing authorization.

7.2.2. PROTECT KIDs ongoing extension

Patients who completed the main PROTECT KIDs study and Part 2 were offered participation in this open-label extension for collection of additional efficacy and safety data and for receipt of at least an additional 50 EDs of BAY 94-9027 or until marketing authorization.

7.3 Select definitions

- **Factor VIII inhibitors:** FVIII inhibitors are inhibitory antibodies directed against FVIII. A FVIII inhibitor of $\geq$0.6 BU/mL was considered a "positive" result. Any positive result was to be confirmed by a recovery level and a second sample.

- **Loss of Efficacy:** "LoE was diagnosed clinically based on unexpected bleeding events, no or inadequate response to treatment of a bleed and reported as 'drug ineffective." (2.7.4 Summary of Clinical Safety, page 9). If FVIII inhibitor was negative, this raised the possibility of anti-drug antibodies.

- **Anti-drug antibodies (ADAs)**: ADAs are binding antibodies against BAY 94-9027 or its PEG moiety. If an ADA was "positive," a FVIII inhibitor was always assessed to exclude a FVIII inhibitor.

- **Hypersensitivity:** The definition of hypersensitivity is derived from the EMA Guideline on core summary of product characteristics for human plasma derived and recombinant coagulation factor VIII products.[1] **"**Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, restlessness,

tachycardia, tightness of the chest, tingling, vomiting, wheezing) […] which may in some cases progress to severe anaphylaxis."[1]

7.4 Notable finding: Immune response to PEG

Immune response to PEG was characterized by development of IgM antibodies against PEG and resulted in LoE (with no evidence of FVIII inhibitors). The risk of LoE and hypersensitivity was primarily identified in individuals <6 years of age and resulted in approximately 23% of patients <6 years of age discontinuing the study (10/44). PEG-related hypersensitivity risk was lower among those aged ≥6 years, resulting in only 3% (1/29) of patients discontinuing the study in this age group. There were no cases of LoE among those ≥6 years of age. In view of these findings and prior discussions with regulatory bodies, the sponsor is seeking approval of BAY 94-9027 only among individuals 12 years of age or older. **As such, the PVP will focus on individuals 12 years of age or older.**

7.5 Deaths

No deaths occurred in the Phase I, PROTECT VIII, or PROTECT KIDs studies.

8 Adverse Events in the Safety Database (individuals ≥12 years of age)

8.1 Description of adverse events

The clinical trials collected information on demographics; medical and disease history, including previous vaccinations and medications; immunogenicity assessments based on FVIII inhibitors, anti-drug antibodies (ADAs) to BAY 94-9027 or its PEG moiety; exposure days to BAY 94-9027; adverse events (AEs); significant adverse events (SAEs); treatment-emergent adverse events (TEAEs); AEs leading to withdrawal from study; general safety laboratory evaluations; and vital signs. All AEs were assessed and documented by the study investigator. Loss of efficacy (LoE) and hypersensitivity (observed in the PROTECT Kids study for patients <6 years of age) were considered AEs of special interest (AESI). The Phase I and PROTECT VIII studies did not define AESIs, and therefore cases of hypersensitivity and LoE were assessed retrospectively.

8.2 Safety database

The safety database was comprised of 148 individuals participating in the Phase I (n=14) and PROTECT VIII (Main and extension) studies (n=134). The median age at study entry was 34.5 years (range, 12-62 years), with 12-17-year old participants comprising 9% (n=13) of the study population. Approximately 68% (n=100), 22% (n=33), and 4% (n=6) of individuals were White, Asian, and Black, respectively (9 patients with unknown race). Nearly 47% of participants were treated in Europe, 32% in North/South America, and 22% in Asia. The mean time in study was 596.5 days (median 713.4 days), and the mean number of EDs was 124.5 days (median 131.0 days). One hundred and three patients (69.6%) had ≥100 EDs.

The most commonly reported medical history at study entry included arthropathy and hepatitis C in 63.5% and 60.1% of 148 study participants, respectively. Among 134 (out of 148) individuals

with information on concomitant medication use, paracetamol (n=84, 56.8%) was the most commonly used medication in the safety population ≥12 years of age.

8.3 Treatment-emergent Adverse Events (Phase I and PROTECT VIII studies)

83.1% of patients (123/148) developed a TEAE, of which 10.1% (15/148) were drug-related, as assessed by the study investigators. The most common MedDRA Preferred terms (PTs) describing TEAEs occurring among more than 5% of the study population are detailed in Table 3. Drug-related TEAEs occurring among more than 1 individual are specified in Table 4.

Table 3. Most commonly occurring (affecting >5% of patients) TEAEs in Phase 1 and PROTECT VIII studies*

	Number of patients	**%**
Total patients	148	100
Total patients with TEAE	123	83.1
Preferred Term		
Nasopharyngitis	33	22.3
Headache	21	14.2
Arthralgia	21	14.2
Back pain	15	10.1
Cough	10	6.8
Upper respiratory tract infection	9	6.1
Epistaxis	9	6.1
Diarrhea	8	5.4
Nausea	8	5.4
Pyrexia	8	5.4
Influenza	8	5.4
Pain in extremity	8	5.4

* Adapted from 2.7.4 Summary of Clinical Safety, Table 2-2.

Table 4. Drug-related TEAEs occurring in at least two patients enrolled In the Phase 1 and PROTECT VIII studies

	Number of patients	%
Total patients	148	100
Total patients with drug-related TEAE	15	10.1
Preferred Term		
Alanine aminotransferase increased	2	1.4
Arthralgia	2	1.4
Headache	2	1.4

* Adapted from 2.7.4 Summary of Clinical Safety, Table 2-3.

Eight (5.4%) out of 148 patients had procedure-related TEAEs represented by the following PTs: vessel puncture site bruise (n=1), vessel puncture site pruritus (n=1), procedural pain (n=1), overdose (also SAE) (n=1), musculoskeletal pain (n=1), myalgia (n=1), paresthesia (n=1), abnormal thinking (n=1), pelvic hemorrhage (also SAE) (n=1), and pruritus (n=1).

A severe TEAE occurred in 24 (16%) of 148 patients. Most PTs occurred in the MedDRA System Organ Class (SOC) for musculoskeletal and connective tissue disorders (n=7); injury, poisoning, and procedural complications (n=6); gastrointestinal disorders (n=4); and infections and infestations (n=3).

Overall 33 (out of 148) individuals developed treatment-emergent SAEs, with PTs that occurred among more than one patient, including hemophilic arthropathy (n=3 patients), device-related infection (n=2 patients), and hemarthrosis (n=2 patients). Four patients developed drug-related treatment-emergent SAEs:

1. Drug hypersensitivity (EDs prior to event = 4); drug withdrawn
2. Overdose (EDs prior to event = 44); drug continued without dose change
3. Liver function tests increased (EDs prior to event = 195); drug withdrawn
4. Back pain, 2 incidents (EDs prior to events = 198 and 204); drug eventually withdrawn

Four out of 148 individuals discontinued the study due to an AE/SAE:

1. Hypersensitivity
2. Drug hypersensitivity
3. Increased liver function test
4. Thrombocytopenia and back pain

8.4 Other Significant Adverse Events

FVIII inhibitors: Factor VIII inhibitor testing with values ≥0.6 Bethesda units (BU)/ml were considered positive; 0.2 BU/ml is the lower limit of detection. Any positive test required confirmation on a different sample. Two patients developed drug-related low titer inhibitors (<5 BU/ml) (one case was not confirmed) and both were in Part B (surgery) treatment arm of PROTECT VIII. Both patients switched to another FVIII product.

Loss of efficacy: As noted above, LoE was assessed retrospectively based on an unexpected bleed or absence of response of a bleed to treatment. Upon retrospective review of bleeding events, none were deemed related to LoE based on review of pre- and post-infusion FVIII levels. None of the bleeding events led to discontinuation from the study.

Reviewer comment: A retrospective assessment may result in underascertainment of cases.

Hypersensitivity reactions: Hypersensitivity reactions were also assessed retrospectively. Three hypersensitivity cases were noted (two of these were serious), as follows:

1. PEG-related hypersensitivity reaction with pre-existing PEG antibodies: 19-year old with asthma who developed transient headache, abdominal pain, dyspnea, flushing, and asthma after 4th dose of BAY 94-9027. This patient had pre-existing anti-PEG antibodies (prior to treatment) and titer increased post-treatment (FVIII inhibitor-negative). Patient declined rechallenge and discontinued the study.

2. Immune response to PEG: 32-year old developed mild and transient flushing, exanthema, and paresthesia during the first dose of BAY 94-9027. The infusion was

stopped and no additional intervention was needed. The patient withdrew consent and discontinued the study.

3. Mild, nonserious, drug hypersensitivity: 33-year old administered BAY 94-9027 for purpose of PK assessment pre-operatively (arthroscopic synovectomy). The patient developed mild flushing, which resolved without further intervention. Of note, this patient had a FVIII inhibitor level of 1.7 BU/ml immediately prior to surgery, and he underwent the procedure with IV steroids and antihistamines to "improve drug tolerance." The post-surgical assessment was deemed to be "moderate" and the patient was switched to another product post-operatively.

9 Sponsor's Pharmacovigilance Plan (PVP)

The sponsor's PVP (Table 5) is based on the document submitted by the sponsor on July 25, 2018 (sequence 0051, module 1.16 Risk Management Plan), with the exception of "Important Identified Risks" which is based on the PVP from the original submission (sequence 0001, module 1.16.1 Risk Management (Non-REMS), table in section 1).

Table 5. Summary table of pharmacovigilance activities and risk minimization activities by safety concern*

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risk		
Development of FVIII inhibitors	**Routine risk minimization measure** • Warning sections 5.2 Neutralizing Antibodies and 5.5 Laboratory Tests • Patient Counselling Information section 17 **Additional risk minimization measure** • None	**Routine pharmacovigilance** • Follow-up questionnaire for adverse reactions (Loss of drug effect) **Additional pharmacovigilance activities** • Interventional post-marketing study to assess safety and efficacy of BAY 94-9027 • EUHASS registry (study 14149)
Hypersensitivity	**Routine risk minimization measure** • Contraindications section 4 • Warning and Precautions section 5.1 Hypersensitivity Reactions and Section 5.3 Immune Response to PEG • Pediatric Use section 8.4 • Patient Counselling Information Section 17 **Additional risk minimization measure** • None	**Routine pharmacovigilance** • Follow-up questionnaire for adverse reactions (Hypersensitivity) **Additional pharmacovigilance activities** • Interventional post-marketing study to assess safety and efficacy of BAY 94-9027 • EUHASS registry (study 14149)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Clinical response characterized by lack of drug effect associated with anti-PEG antibodies	**Routine risk minimization measure** • Indications and Usage Section 1 • Warning and Precautions section 5.1 Hypersensitivity Reactions and Section 5.3 Immune Response to PEG • Pediatric Use Section 8.4 • Description Section 11 • Patient Counselling Information Section 17 **Additional risk minimization measure** • Communication plan	**Routine pharmacovigilance** • Follow-up questionnaire for adverse reactions(Loss of drug effect) **Additional pharmacovigilance activities** • Interventional post-marketing study to assess safety and efficacy of BAY 94-9027
Important potential risks		
N/A		
Missing information		
Potential long-term PEG-related adverse reactions	**Routine risk minimization measure** • Nonclinical Toxicology Section 13 **Additional risk minimization measure** • None	**Routine pharmacovigilance** • Follow-up questionnaire for adverse reactions (Renal Impairment) **Additional pharmacovigilance activities** • EUHASS registry (study 14149)
Use in patients with severe hepatic impairment	**Routine risk minimization measure** • Not included in USPI **Additional risk minimization measure** • None	**Routine pharmacovigilance** **Additional pharmacovigilance activities** • None
Use in patients with severe renal impairment	**Routine risk minimization measure** • Not included in USPI **Additional risk minimization measure** • None	**Routine pharmacovigilance** **Additional pharmacovigilance activities** • None
Use in elderly patients >65 years of age	**Routine risk minimization measure** • Geriatric Use Section 8.5 **Additional risk minimization measure** • None	**Routine pharmacovigilance** **Additional pharmacovigilance activities** • None

* Based on PVP submitted by the sponsor on July 25, 2018 (sequence 0051, module 1.16 Risk Management Plan).

9.1 Important identified risks

9.1.1 Development of Factor VIII inhibitors

Two patients developed drug-related low titer inhibitors (<5 BU/ml) (one case was not confirmed). Factor VIII inhibitors are a known risk associated with this class of products. In addition to routine pharmacovigilance, the sponsor has proposed the following pharmacovigilance activities to address this important identified risk:

Questionnaire: Factor VIII inhibitors occurred rarely in the Phase I/PROTECT VIII studies but did result in two patients discontinuing study participation. In addition to routine pharmacovigilance, the sponsor has created an "LoE" questionnaire for providers to complete on patients who report this AE so that additional information can be gathered regarding inhibitor development.

> *Reviewer assessment*: Development of Factor VIII inhibitors is a rare but known risk associated with FVIII products (class effect). Supporting this is the finding that two patients developed drug-related, low titer FVIII inhibitors and discontinued treatment with BAY 94-9027. Because of the rare occurrence of FVIII inhibitors and known association with FVIII products, the sponsor's plan for risk minimization through the product label (USPI) is appropriate. The plan for routine pharmacovigilance and to utilize a questionnaire to gather further details on patients who develop inhibitors, including potential risk factors, and inhibitor-associated lab values, is acceptable. One of the limitations associated with passive surveillance is that only a fraction of individuals who develop FVIII inhibitors will likely be reported to the sponsor. In addition, completion of questionnaires by providers is not mandatory, and among those cases reported to the sponsor, only a fraction are likely to have questionnaires completed by the provider.

Post-marketing study: The sponsor is proposing a phase IV interventional, open label, non-controlled study of at least 25 previously treated male patients ≥12 years of age with severe hemophilia A. This study is being undertaken to meet the target of 200 patients achieving 100 EDs based on prior agreement with the EMA that a total of 200 patients need to complete 100 exposure days. As of February 2017, 161 patients had achieved >100 EDs, and it was expected that another 9-10 patients would do so by the end of 2018. Therefore, the proposed participant number (at least 25) will meet the 200-participant/100-ED requirement of the EMA.

> *Reviewer assessment:* A detailed study protocol is not available but a synopsis was provided. While this study will allow for additional monitoring of FVIII inhibitor development, hypersensitivity and other AEs, by itself – given the possibility of only 25 patients participating – this study alone will not likely be able to detect rare outcomes, including inhibitors, LoE, and hypersensitivity. A final study protocol will need to be submitted for FDA review prior to patient enrollment. In addition, an analysis plan will need to include power calculations and clarify how this study will be analyzed (e.g., separately or in conjunction with prior studies) since the goal is to assess 200 patients treated over the long-term (>100 EDs). Therefore, the study protocol will need to reflect the analysis plan.

In brief, the objectives of the study are to collect information on safety and efficacy to assure that post-marketing findings are consistent with those from pre-marketing trials. Previously treated patients (>150 EDs) who have not been exposed to BAY 94-9027 will be treated with BAY 94-9027 every 5 days (60 IU/kg), twice weekly (40 IU/kg), or every 7 days (60 IU/kg) up to

a maximum of 6000 IU and will be followed for the time needed to reach 100 EDs. Safety endpoints include adverse events, FVIII inhibitor development, ADAs against BAY 94-9027, and concomitant medications. Laboratory testing (frequency not specified) will include hematology, chemistry (creatinine, calculated creatinine clearance, AST, ALT), biomarkers (e.g., Kim-1), urine biomarkers (total protein, albumin, alpha-2 microglobulin, Kim-1). Inclusion criteria include HIV negative or immunocompetent individuals with aCD4 lymphocyte count >200/µl.

Reviewer assessment: There is no indication in the study synopsis whether individuals with impaired hepatic or renal impairment will be excluded.

The European Haemophilia Safety Surveillance System (EUHASS): This registry is an adverse event reporting system for Europe that involves prospective AE reporting in patients with hemophilia A and other rare inherited bleeding disorders. AEs collected in EUHASS include:

- Allergic or other acute events
- Transfusion-transmitted infections
- Inhibitors
- Unexpected poor efficacy
- Thromboses
- New cardiovascular events
- New malignancy
- Deaths
- Other AEs possibly related to concentrate
- Neurologic events (this category was added in February 2018)

Reviewer assessment: The EUHASS registry is an adverse event reporting system for Europe that involves prospective adverse event reporting in patients with hemophilia A and other rare inherited bleeding disorders. While this reporting is encouraged, the EUHASS registry does not fulfill U.S. reporting requirements, does not include U.S. patients, and product-specific information may be limited. Nevertheless, EUHASS represents an additional resource to gather information on inhibitor development. Because reporting to EUHASS is not compulsory, the registry is associated with some of the same limitations as other passive surveillance systems.

9.1.2 Hypersensitivity

Hypersensitivity was observed in three patients in the Phase I/PROTECT VIII studies (although assessed retrospectively), of which two events were serious. In addition to routine pharmacovigilance, the sponsor has proposed a "Hypersensitivity" questionnaire that will be given to providers for patients reporting these AEs so that additional information can be gathered regarding hypersensitivity development. In addition, the sponsor proposes to study at least 25 previously treated male patients in a post-marketing phase IV interventional, open label, noncontrolled study of additional patients and EUHASS registry (as described above).

Reviewer assessment: Hypersensitivity is a rare but known risk associated with FVIII products (class effect). Because of the rare occurrence of hypersensitivity and known association with FVIII products, the sponsor's plan for risk minimization through the

product label (USPI) is appropriate. The sponsor's plan for routine pharmacovigilance and for administering a questionnaire to gather further details on patients who develop hypersensitivity and potential associated risk factors, is acceptable. One of the limitations associated with passive surveillance is that only a fraction of individuals who develop hypersensitivity will likely be reported to the sponsor. In addition, completion of questionnaires by providers is not mandatory, and among those cases reported to the sponsor, only a fraction are likely to have questionnaires completed by the provider.

Post-marketing study: While this study will allow for additional monitoring of hypersensitivity and other AEs, by itself – given the possibility of only 25 patients participating – this study will not likely be able to detect rare outcomes, such as hypersensitivity. A final study protocol will need to be submitted for FDA review prior to patient enrollment. In addition, an analysis plan will need to include power calculations and clarify how this study will be analyzed (e.g., separately or in conjunction with prior studies) since the goal is to assess 200 patients treated over the long-term (>100 EDs). Therefore, the study protocol will need to reflect the analysis plan.

EUHASS: The EUHASS registry is an adverse event reporting system for Europe that involves prospective adverse event reporting in patients with hemophilia A and other rare inherited bleeding disorders. While this reporting is encouraged, the EUHASS registry does not fulfill U.S. reporting requirements, does not include U.S. patients, and product-specific information may be limited. Nevertheless, EUHASS represents an additional resource to gather information on inhibitor development. Because reporting to EUHASS is not compulsory, the registry is associated with some of the same limitations as other passive surveillance systems.

9.1.3 Lack of drug effect (LoE)

LoE was assessed retrospectively in the Phase I and PROTECT VIII studies based on an unexpected bleed or absence of response of a bleed to treatment. Upon retrospective review of bleeding events, none were deemed related to LoE based on review of pre- and post-infusion FVIII levels. In addition to routine pharmacovigilance, the sponsor has proposed use of an LoE questionnaire that will be given to providers to complete on patients reporting this AE so that additional information can be gathered regarding LoE. In addition, the sponsor proposes to study at least 25 previously treated male patients in a post-marketing phase IV interventional, open label, noncontrolled study of additional patients.

Reviewer assessment: The clinical manifestations of LoE due to anti-PEG antibodies are identical to those of a Factor VIII inhibitor, with the exception that laboratory evaluation will yield a negative FVIII inhibitor level. Unlike FVIII inhibitors, it is unlikely that the general provider will have access to anti-BAY 94-9027 and anti-PEG testing, as this is not routinely performed in patients with hemophilia A (not standard of care), and therefore determining the etiology of specific LoE cases may be limited. In addition, testing for anti-PEG antibodies at the start of therapy will not likely be accomplished, so understanding the relationship between pre- and post-treatment PEG levels will be limited. While this might be considered an academic point, developing a greater understanding of risk factors for LoE might be helpful to identify individuals at highest risk to potentially avoid exposures.

Because of the rare occurrence of LoE, the sponsor's plan for risk minimization through the USPI is appropriate. Furthermore, the plan for routine pharmacovigilance and use of a questionnaire to gather further details on patients who develop LoE and potentially associated risk factors, is adequate. As noted, one of the limitations associated with passive surveillance is that only a fraction of individuals who develop LoE will likely be reported to the sponsor. In addition, completion of questionnaires by providers is not mandatory, and among those cases reported to the sponsor, only a fraction are likely to have questionnaires completed by the provider.

Post-marketing study: While this study will allow for additional monitoring of LoE and other AEs, by itself – given the possibility of only 25 patients participating – this study will not likely have sufficient power to detect rare outcomes, such as LoE. A final study protocol will need to be submitted for FDA review prior to patient enrollment. In addition, an analysis plan will need to include power calculations and clarify how this study will be analyzed (e.g., separately or in conjunction with prior studies) since the goal is to assess 200 patients treated over the long-term (>100 EDs). Therefore, the study protocol will need to reflect the analysis plan.

9.2 Important potential risks: None identified

The sponsor has not identified any important potential risks.

Reviewer assessment: If approved, BAY 94-9027 would be the first FVIII product to be associated with an age restriction, reflecting the frequency of occurrence of LoE and hypersensitivity among previously treated patients <12 years of age, and most prominently among those <6 years of age. As such, off-label use of BAY 94-9027 in children <12 years of age is considered an important potential risk if providers intentionally or unintentionally prescribe the product to a patient <12 years of age. However, the age indication is included on the USPI, and providers will need to be informed about the product and, if they elect to treat patients <12 years of age, weigh the risks and benefits of treatment. The sponsor has outlined a communication plan to inform providers about the age restriction associated with BAY94-9027, and it will be important to ensure that the information is effectively disseminated. Routine pharmacovigilance activities will contribute to the assessment of AEs occurring among patients <12 years of age, and may help inform the sponsor about the effectiveness of its communication plan.

9.3 Missing information

9.3.1 Potential long-term PEG-related effects

The sponsor proposes to include information in the USPI (Nonclinical Toxicology). In addition, the sponsor will undertake routine pharmacovigilance, follow-up questionnaire (Renal), and reporting to the EUHASS registry.

Reviewer assessment: While the sponsor indicates that the risk of PEG accumulation with long-term use of BAY 94-9027 is very low and the sponsor's 26-week pre-clinical study in immunodeficient male rats did not demonstrate PEG accumulation in the kidney, they propose to institute a questionnaire to assess patients who develop renal

impairment during treatment. The sponsor indicates that urinary excretion of PEG has been demonstrated in nonclinical studies reported in the literature. The implementation of a renal questionnaire is reasonable.

As noted above, the Phase I and PROTECT VIII studies excluded individuals with renal impairment, and similarly those with hepatic impairment. The accumulation of PEG in the liver is an equally relevant concern to PEG accumulation in the kidney, in part because hemophilia patients may have a concurrent diagnosis of hepatitis and exposure to hepatotoxins (e.g., alcohol, medications) that is difficult to reproduce in animal model studies. In addition, while no patients treated with BAY 94-9027 developed TEAEs related to renal dysfunction, one patient discontinued BAY 94-9027 and study participation after developing a treatment-emergent SAE related to elevation in liver enzymes. In the literature, other PEG-containing products have shown PEG accumulation in the liver.[2,3] Specifically, radiolabeled PEG activity was measured in Hemophilia A mice (80 IU/kg) injected with ^{125}I-labelled, pegylated (60 kDa branched molecule) FVIII every three days for a total of 4 doses and compared to mice administered a single dose. In these mice, the highest radioactivity was measured in the liver (versus other organs including spleen and muscle), and significantly higher ^{125}I activity was noted at 24-hours among the mice treated with repeated doses compared to the single dose – 26.3% versus 15.7%, respectively.[2] Based on the aforementioned information, a "hepatic questionnaire" aimed at further studying individuals who develop hepatic impairment on therapy with BAY 94-9027 is suggested.

EUHASS: As noted above, the EUHASS registry is an adverse event reporting system for Europe that involves prospective adverse event reporting in patients with hemophilia A and other rare inherited bleeding disorders. While this reporting is encouraged, the EUHASS registry does not fulfill U.S. reporting requirements and does not include U.S. patients. Nevertheless, EUHASS represents an additional resource to gather information on important AEs. Because reporting to EUHASS is not compulsory, the registry is associated with some of the same limitations as other passive surveillance systems.

9.3.3 Use in patients with severe hepatic impairment

The sponsor does not have any proposed risk minimization measures for patients with hepatic impairment and plans to undertake routine pharmacovigilance activities.

Reviewer assessment: As noted above, patients with severe hepatic impairment were excluded from the Phase I/PROTECT VIII clinical trials. While routine pharmacovigilance activities are reasonable, given the potential for PEG accumulation in the liver with long-term use, a hepatic questionnaire is suggested to more consistently gather additional information on those who develop hepatic impairment on BAY 94-9027 (refer to section 9.3.1 "Potential long-term PEG-related effects" above).

9.3.4 Use in patients with severe renal impairment

The sponsor does not have any proposed risk minimization measures for patients with renal impairment and plans to undertake routine pharmacovigilance activities.

Reviewer assessment: As noted above, patients with severe renal impairment were excluded from the Phase I/PROTECT VIII clinical trials. While routine pharmacovigilance activities are reasonable, given the concern for PEG accumulation in the kidney with long-term use, a renal questionnaire has been developed to gather additional information on those who develop renal impairment on BAY 94-9027 (refer to section 9.3.1 "Potential long-term PEG-related effects" above).

9.3.5 Use in elderly patients >65 years of age

The sponsor's proposed risk minimization measures relate to inclusion of information on the USPI (Geriatric Use, section 8.5). Routine pharmacovigilance is planned.

Reviewer assessment: There are no data on use of BAY 94-9027 in patients >65 years of age. This reviewer agrees that the risk minimization measures and routine pharmacovigilance to carefully assess AE reports submitted among older individuals is appropriate.

10. Conclusions and recommendations

- The sponsor's PVP adequately reflects most safety concerns. Comments and recommendations are summarized in Table 6 below.

- Providers in Europe are encouraged to submit reports of AEs to the EUHASS registry, but this registry does not include U.S. patients and is inclusive of all factor products used to treat the pre-specified bleeding disorders, inclusive of hemophilia A. Therefore, the PVP for BAY 94-9027 use in the U.S. cannot be dependent on reporting AEs to the EUHASS registry.

Table 6. Reviewer comments and required actions for PVP for BAY 94-9027

Risk	**Pharmacovigilance actions**
Important identified risks	
• Development of FVIII inhibitors • Hypersensitivity • LoE associated with anti-drug antibodies (including anti-PEG antibodies)	*Comment*: 1. Agree with sponsor's plan to include information in the USPI to undertake routine pharmacovigilance, and to administer AE-specific questionnaires (LoE, hypersensitivity). 2. Agree with interventional post-marketing study to assess safety and efficacy of BAY 94-9027, as previously agreed upon by regulatory agencies. ***Required Actions****:* **1.** With each required Periodic Surveillance Report (PSUR) submitted to FDA*, the sponsor is requested to summarize and discuss LoE and hypersensitivity questionnaire data for the period under study and cumulatively; the annual PSUR should analyze and assess questionnaire data for the period under study and cumulatively. Each PSUR should include dose distribution data (for calculation of reporting rates over time).

Risk	Pharmacovigilance actions
	2. A protocol and analysis plan for the proposed post-marketing study will need to be submitted to FDA for review prior to study initiation.
Important potential risks	
• None identified by sponsor. [Per this reviewer: AEs occurring among children <12 years of age]	***Required Action****:* **1.** Routine pharmacovigilance to assess AEs occurring among children <12 years of age and reporting this information (for period under study and cumulatively) with each required PSUR.
Missing information	
• Potential long-term PEG-related adverse reactions • Use in patients with severe hepatic impairment • Use in patients with severe renal impairment • Use in elderly patients >65 years	*Comment*: Agree with the sponsor's plan to include information in the USPI and to undertake routine pharmacovigilance and to administer the renal questionnaire for those who develop renal impairment on therapy with BAY 94-9027. Development of a hepatic questionnaire is recommended to further study patients who develop hepatic impairment on therapy. ***Required Actions****:* **1.** With each required PSUR submitted to FDA*, the sponsor is requested to summarize and discuss renal and hepatic questionnaire data for the period under study and cumulatively; the annual PSUR should analyze and assess questionnaire data for the period under study and cumulatively. Each PSUR should include dose distribution data (for calculation of reporting rates over time).

* As required under 21 CFR 600.80.

10 References:

1. EMA. Guideline on core SmPC for human plasma derived and recombinant coagulation factor VIII products. Vol. EMA/CHMP/BPWP/1619/1999 rev 2. United Kingdom: European Medicines Agency; 2016.
2. Hong VP, Ismail A, Moore N, Peters R, Salas J. Novel Approach to Study Biodistribution and Accumulation of Pegylated Recombinant Factor VIII in Haemophilia A Mice. *Blood*. 2015;126(23).
3. Ivens IA, Achanzar W, Baumann A, et al. PEGylated Biopharmaceuticals: Current Experience and Considerations for Nonclinical Development. *Toxicol Pathol*. 2015;43(7):959-983.