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Summary Basis for Regulatory Action

Date: August 29, 2018

From: Zuben Sauna, PhD

BLA STN#: 125661/0

Applicant Name: Bayer Healthcare, Inc

Date of Submission: August 30, 2017

Goal Date: August 30, 2018

Proprietary Name: JIVI

Proper Name: antihemophilic factor (recombinant), PEGylated-aucl

Indication: Indicated for use in previously treated adults and adolescents (12 years of age and older) with hemophilia A (congenital Factor VIII deficiency) for: on-demand treatment and control of bleeding episodes; perioperative management of bleeding; and routine prophylaxis to reduce the frequency of bleeding episodes.

Limitations of Use
JIVI is not indicated for use in children < 12 years of age due to greater risk for hypersensitivity reactions. JIVI is not indicated for use in previously untreated patients (PUPs).
JIVI is not indicated for the treatment of von Willebrand disease.

Recommended Action:
The Review Committee recommends approval of this Biologics License Application.

Review Office Signatory Authority:

Wilson W. Bryan, MD
Director
Office of Tissues and Advanced Therapies

☒ I concur with the summary review.

☐ I concur with the summary review and include a separate review to add further analysis.

☐ I do not concur with the summary review and include a separate review.

The table below indicates the material reviewed when developing the SBRA

Discipline	**Reviewer name**
CMC Review(s) • *CMC (product office)*	Zuben Sauna, Ph.D., OTAT/DPPT/HB Ze Peng, Ph.D., OTAT/DPPT/HB Daniel Lagasse, Ph.D., OTAT/DPPT/HB
• *Facilities review (OCBQ/DMPQ)*	Lori Peters, MS, OCBQ/DMPQ/B1
QC, Sterility and Endotoxin	Hyesuk Kong, PhD, OCBQ/DBSQC/LMIVTS Parmesh Dutt, PhD, OBRR/DBCD/BPB
QC, Test Methods, Product Quality	Ritu Agarwal, PhD, OCBQ/DBSQC/LACBRP Hsiaoling Wang, PhD, OCBQ/DBSQC/LACBRP
Lot Release Protocol/Testing Plan	Varsha Garnepudi, PhD, OCBQ/DBSQC/QAB
Clinical Review(s) • *Clinical (product office)*	Megha Kaushal, MD, OTAT/DCEPT/CHB Bindu George, MD, OTAT/DCEPT/CHB
• *Postmarketing safety epidemiological review (OBE/DE)*	Graca Dores, M.D., OBE/DE/AEB
• *BIMO*	Bhanumathi Kannan, MS, OCBQ/DIS/BMB
Statistical Review(s) • *Clinical data* • *Non-clinical data*	Lin Huo, PhD, OBE/DB/TEB
Pharmacology/Toxicology Review(s) • *Toxicology (product office)*	Sandhya Sanduja, PhD, OTAT/DCEPT/PTB1
Clinical Pharmacology Review(s)	Iftekhar Mahmood PhD, OTAT/DCEPT/GMBII
Labeling Review(s) • *APLB (OCBQ/APLB)*	Oluchi Elekwachi, PharmD, OCBQ/DCM/APLB Kristine Khuc, PharmD, OCBQ/DCM/APLB
• Regulatory Project Management	Candace Jarvis, OTAT/DRPM/BR2 Kay Owosela, MS, OTAT/DRPM/BR1

1. INTRODUCTION

Bayer Healthcare, LLC (Bayer) submitted an original Biologics License Application (BLA) to seek U.S. licensure for antihemophilic factor (recombinant), PEGylated-aucl. For this product, the applicant also uses the International Nonproprietary Name,

damoctocog alfa pegol, as well as its code name, BAY 94-9027. The proprietary name of the U.S. marketed product will be JIVI. JIVI is a lyophilized powder available in nominal dosage strengths of 500, 1000, 2000, or 3000 international units (IU) of Factor VIII (FVIII) activity. The product is reconstituted with sterile Water for Injection (sWFI) for intravenous administration.

The active ingredient of JIVI is a B-domain-deleted (BDD) recombinant (r) FVIII protein conjugated with a single 60-kDa branched polyethylene glycol (PEG) molecule at a specific cysteine residue introduced at position (b) (4) (position 1804 in the full-length FVIII sequence, K1804C). This product is expressed in a BHK(b) (4) cell line. JIVI shows a comparable mechanism of action to that of other rFVIII products but with a prolonged plasma half-life of (b) (4) .

The proposed indication is for use in previously treated adults and adolescents (12 years of age and older) with hemophilia A (congenital Factor VIII deficiency) for:
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes

To support the proposed indication, the BLA includes results from two single-arm studies:

a) Study 1: A study to evaluate the efficacy and safety of JIVI for on-demand, routine prophylaxis and perioperative management in adults and adolescents (≥12 years of age) with severe hemophilia A.
b) Study 2: A study to evaluate the efficacy and safety of JIVI for treatment of bleeding and routine prophylaxis in previously treated pediatric patients (<12 years of age) with severe hemophilia A.

The applicant does not wish to seek any indication in pediatric patients although the PREA requirements were met.

Study 1 is an adequate and well-controlled study that demonstrates efficacy of JIVI for on-demand, routine prophylaxis and perioperative management of patients with severe hemophilia A with an acceptable safety profile and favorable benefit-risk assessment. The data from Study 2 raises safety concerns related to development of hypersensitivity reactions and development of anti-PEG antibodies in pediatric subjects < 12 years of age. Therefore, the label will address the safety concerns in pediatric patients through the Limitations of Use and Warnings and Precautions sections of the label.

2. BACKGROUND

Hemophilia A is a rare hereditary hematologic disorder caused by deficiency or dysfunction of Coagulation FVIII (historically referred to as Antihemophilic Factor), resulting in bleeding secondary to abnormal clot formation. Hemophilia A has an X-linked, recessive inheritance pattern affecting 1 in 5,000 male births with rare occurrence in females. Severity of hemophilia is classified based on a FVIII level with severe hemophilia being defined as <1% functional activity (1 IU/dL) and moderate

hemophilia as FVIII levels that range from 1-5% (1-5 IU/dL). Replacement therapy is generally warranted for patients with severe hemophilia or moderate hemophilia with the severe bleeding phenotype to reduce long-term joint damage from hemarthropathy, and to reduce the frequency of or to treat life-threatening bleeding. Patients with hemophilia A are treated by intravenous administration of plasma-derived or recombinant FVIII products, either full-length or B-domain-deleted.

Most clinical trials to evaluate efficacy and safety of replacement therapy either as a) on-demand treatment to control bleeding episodes; b) routine prophylaxis to reduce the frequency of bleeding particularly spontaneous bleeding; or c) peri-operative management to reduce or prevent excessive bleeding during major and minor surgeries, have enrolled mostly male subjects with severe hemophilia or moderate hemophilia with severe bleeding phenotypes. Currently there are over 10 licensed plasma-derived or recombinant FVIII products for the treatment of severe hemophilia.

The FVIII products described above all require frequent infusions when used for routine prophylaxis. Consequently, extended half-life products have been developed. Several platform technologies have been used to extend the plasma half-life of therapeutic FVIII proteins, in the case of JIVI this involves the addition of a PEG moiety to the active molecule.

The development of neutralizing anti-drug antibodies (often called "inhibitors" in the coagulation literature) occurs in ~30 - 35% of previously-untreated patients (PUPs). This is the most serious complication in the management of hemophilia A, and represents a major source of morbidity and mortality. The neutralizing anti-drug antibodies to a particular product often, though not always, cross-react with other FVIII products, as well as the patient's endogenous FVIII. When therapeutic proteins are engineered, and neo-sequences introduced (e.g., the amino-acid substitution, and the novel linker region while generating the BDD in this product) there are additional immunogenicity concerns. Similarly, the added PEG moiety could potentially also elicit immune responses. These different product-specific immune responses, which include hypersensitivity, have been evaluated in the review of JIVI.

Regulatory History

The BLA was received by FDA on August 31, 2017, and reviewed under the standard (12-month) review schedule of the PDUFA V program. The milestones are listed in the table below:

Milestone	*Date*
Received	August 31, 2017
Committee assignment	September 20, 2017
Filing date	October 23, 2017
Proprietary name review	October 17, 2017
Facility Inspections	Waived
Mid-cycle communication	February 26, 2018
Late-cycle meeting	May 29, 2018

Action Due Date	August 30, 2018

The evidence for safety and effectiveness for this product was collected under IND 14369. Key interactions were held with the FDA throughout the development process as listed in the table below:

Interaction/Correspondence	*Date*
Type C meeting (CRMTS 6951)	March 5, 2009
Follow up Teleconference	June 17, 2009
Type C meeting (CRMTS 7291)	January 12, 2010
Type C meeting (CRMTS 7901)	May 3, 2011
Teleconference denial of Type B EOP2 meeting request	October 3, 2011
Type C meeting (CRMTS 10427)	November 8, 2016
Type C meeting (CRMTS 10476)	December 6, 2016
Type B pre-BLA meeting (CRMTS 10668)	May 31, 2017
FDA comments on proposed chronic toxicity study	July 27, 2017
Teleconference BLA submission plan	August 16, 2017

Regulatory Background for the Clinical Development Program
In a teleconference with Bayer on June 17, 2009, FDA agreed that a comparator study or arm would not be required. FDA also agreed that a single pharmacokinetic (PK) study to evaluate dosing frequency and dose to maintain FVIII levels > 1% would be conducted and a multi-center Phase 2-3 open-label single-arm study would be conducted to evaluate the efficacy and safety of JIVI.

In a Type C meeting held on November 8, 2016, FDA conveyed that the hypothesis testing plan and the plan to determine the efficacy of the three dosing regimens evaluated in the Phase 3 study should be discussed in a pre-Biologics License Application (BLA) meeting. FDA also conveyed that the preliminary data raised safety concerns regarding development of hypersensitivity reactions, and development of anti-PEG antibodies with loss of efficacy, and that these would be further explored at the time of the BLA review.

During the pre-BLA meeting on June 28, 2017, an agreement was reached as to the data to be submitted under the integrated safety summary (ISS), the extent of anti-PEG antibody and FVIII antibody testing and the assays used and classification of the antibody by immunoglobulin sub-type. An agreement was also reached regarding the timing of submission of the results of pre-clinical studies to evaluate the safety of PEG moiety.

3. CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

Description
JIVI is a sterile, nonpyrogenic, preservative-free, white to slightly yellow lyophilized powder for reconstitution with 2.5 mL sWFI as diluent for intravenous (IV) infusion. After reconstitution, the solution appears as a clear and colorless liquid, free of visible

particles, and contains the following excipients (per vial): glycine, 59 mg; sucrose, 27 mg; histidine, 8.4 mg; sodium chloride, 4.7 mg; calcium chloride (b) (4) ; and polysorbate 80, 216 µg. JIVI is available in single-use vials containing the labelled amount of Factor VIII activity, expressed in international units. Each vial contains nominally 500 IU, 1000 IU, 2000 IU or 3000 IU. JIVI potency is assigned using an *in vitro* chromogenic substrate assay calibrated against the World Health Organization (WHO) international standard for Factor VIII concentrates. JIVI contains no preservatives.

JIVI is a recombinant analog of BDD FVIII with an engineered amino acid substitution (K1804C) within the A3 domain. This mutation provides a (b) (4) 60-kDa branched PEG moiety via maleimide conjugation. The BDD-FVIII moiety is comprised of a (b) (4) and a (b) (4) Including glycosylation and PEGylation, the approximate molecular mass of JIVI is 234 kDa. JIVI is expressed in a BHK(b) (4) cell line, which is (b) (4) used for the manufacture of the two licensed Bayer rFVIII products - KOGENATE FS, and KOVALTRY. Functional characterization of JIVI shows comparable mechanism of action to that of other rFVIII products, but with a prolonged plasma half-life (b) (4) vs. (b) (4)).

Analytical Characterization
Characterization of the JIVI primary structure has revealed that the molecule has the expected profile for protein size distribution, protein backbone sequence and mass. In addition, JIVI characterization has confirmed the identity of (b) (4) .

While there is a potential risk for introducing (b) (4) B-domain in JIVI is consistent with other approved BDD-rFVIII products.

Most of the cysteine (b) (4) in JIVI (b) (4) ; however, (b) (4) cysteines exist in addition to C1804 (engineered target site for PEGylation) (b) (4) -C1804 (b) (4) cysteines have the potential to be (b) (4) . To assess the homogeneity of JIVI, PEGylation site identification was conducted by (b) (4) . A PEGylated peptide containing C1804 was the (b) (4) PEGylated peptides were also identified, including (b) (4) (b) (4) . These characterization studies demonstrate that most of the PEGylation occurs at the intended site, however, heterogeneity does exist. While the (b) (4) PEGylation sites are (b) (4) , any significant deviations have the potential to affect potency and safety. No structural differences were observed between the clinical and conformance lots.

JIVI has the expected (b) (4) relative to the reference standard. Bayer observed consistency of the (b) (4) between clinical and conformance lots. The expected (b) (4) have been confirmed. (b) (4) were consistently detected in clinical and conformance lots. No (b) (4) was detected in clinical and conformance lots. Characterization of (b) (4) from

JIVI have shown consistency of structures present between the reference standard, clinical and conformance lots.

Impurities
Adequate removal of product and process-related impurities by the commercial manufacturing process was demonstrated during process development and process validation. The clearance of impurities to levels substantially lower than established permitted daily exposure (PDE) limits supports a clear safety margin. Compounds for which a PDE limit is not established were considered safe since clinical studies presented no associated adverse events.

Residual amounts of the following process and product-related impurities were characterized and monitored in the drug substance or drug product:

(b) (4) /cell culture-related impurities

- (b) (4)

Purification process-related impurities

- (b) (4)

Product-related impurities

- (b) (4)

Drug Product Release Specification
The release specifications, and the justifications, provided in the table below are considered adequate to confirm product quality and manufacturing consistency.

Final drug product specifications:

Analytical method	Specification				Justification
	500 IU/vial	1000 IU/vial	2000 IU/vial	3000 IU/vial	
Visual before reconstitution	White to slightly yellow				These release specifications were based on the historical range for clinical Phase 3 data and the release specifications for rFVIII-FS
Visual after reconstitution	Clear liquid				
Clarity	(b) (4)				
Color determination	(b) (4)				
Solubility time	(b) (4)				
pH	6.6 to 7.0				
(b) (4)	(b) (4)				
Moisture (%)	(b) (4)				
Particulate Matter Number of Particles/vial (b) (4)	(b) (4)				
Particulate Matter Number of Particles/vial (b) (4)	(b) (4)				
Purity	(b) (4)				Statistical analyses* of manufacturing data from (b) (4) Phase 3 clinical batches and (b) (conformance batches (b) (4) were used to justify specifications. (b) (4)
(b) (4)	(b) (4)				
(b) (4)	(b) (4)				
(b) (4)	(b) (4)				
Potency (IU/vial), minimum	(b) (4)				
Potency (IU/mL) minimum	(b) (4)				
Specific Activity	(b) (4)				
Total protein (µg/vial)	(b) (4)			(b) (4)	
Total protein (µg/mL)				(b) (4)	
Sterility	No microbial growth observed (b) (4)				Based on the historical range for release specifications for rFVIII-FS
Endotoxin (b) (4) (b) (4)	(b) (4)				
Glycine	(b) (4)				(b) (4)
Histidine	(b) (4)				
Sucrose	(b) (4)				
Sodium	(b) (4)				
Calcium	(b) (4)				
Polysorbate 80	(b) (4)				

(b) (4)

Process Description

The manufacturing process of JIVI starts by (b) (4) The filled vials are stoppered and capped under controlled aseptic conditions, and visually inspected. Final vials are then packaged, delivered to the warehouse and stored at 2 to 8°C until shipped.

Critical process steps, parameters and their control
The critical control parameters for the JIVI manufacturing process are adequate. The action limits based on historical data and experience can assure product quality.

The following process parameters were deemed critical during the manufacture of JIVI:

Process steps	Critical Process Parameters	Acceptance criteria
(b) (4)		

1 page has been determined to be not releasable: (b)(4)

(b) (4)

Drug Product		
Preparation of (b) (4)		
(b) (4) drug substance	(b) (4)	
Preparation of sterile final bulk	(b) (4)	
Filling	(b) (4)	
Freeze drying	(b) (4)	

(b) (4)

Process validation
Full-scale conformance lots were manufactured to demonstrate the JIVI manufacturing process is robust and reproducible, can be maintained within established parameters, and consistently produces product meeting all predetermined in-process control limits, release specifications, and quality attributes. No changes were made in the manufacturing process, facilities and equipment between lots used in the Phase 3 clinical trials and conformance lots. The DP conformance lots were manufactured from QA released conformance (b) (4) DP from the conformance lots were placed on real-time and accelerated stability programs.

Conformance lots manufacture
For the commercial conformance campaign, (b) (4) DP lots were manufactured at the proposed commercial manufacturing site (Bayer (b) (4) Batch genealogy is available for all lots, providing traceability from raw materials to final container. The DP lot numbers and dates of manufacture of the commercial conformance lots are summarized as follows:

(b) (4)

All commercial conformance DP lots met release criteria and support consistency of product manufacture.

Viral Testing Controls and Clearance
The viral safety evaluation on JIVI is as follows:

1) Control of non-viral adventitious agents

For the non-viral adventitious agents including bacteria, fungi, and mycoplasma, the potential of contamination of these agents is adequately controlled through the use of:

(1) appropriate environmental monitoring in the manufacturing process; (2) in-process controls, e.g., testing for microbial growth and mycoplasma in (b) (4) ; and (3) filtration steps including (b) (4) sterile filtration. The potential of JIVI to be contaminated with non-viral adventitious agents is further reduced by testing the FDP for Sterility, and Endotoxin. Bayer manufactures JIVI according to cGMP regulations.

No human- or animal-derived raw materials are used in the manufacture of JIVI. Additionally, routine cleaning procedures in the manufacturing process of JIVI include sanitization of equipment with (b) (4) , for the removal and/or inactivation of potential contaminations of viruses. Thus, the potential risk of contaminating adventitious viruses or transmissible spongiform encephalopathy agents is minimized.

2) Testing the capacity of the JIVI purification process to clear viruses

There are (b) (4) dedicated, (b) (4) steps for viral clearance in the manufacturing process of JIVI, which are (b) (4) These viruses resemble viruses which may contaminate the JIVI product, and represent a wide range of physico-chemical properties that tests the ability of the manufacturing process to eliminate viruses. Virus clearance studies were performed by (b) (4) Virus inactivation and/or removal by the respective step(s) were tested at least (b) (4). Down-scale studies on the relevant steps resulted in at least the following overall log reduction factors, in parentheses, for these viruses: (b) (4) . These results are supportive of the effectiveness of the manufacturing process in viral clearance.

Analytical Methods
The analytical methods and their validations and/or qualifications reviewed for the JIVI DS and DP were found to be adequate for their intended use.

The potency of JIVI is measured using a chromogenic substrate assay for FVIII activity. Potency measured in the chromogenic assay was the primary stability-indicating parameter for JIVI. The JIVI formulation was assessed to meet a minimum shelf-life target of (b) (4) of the initial potency under the intended storage conditions (24 months at 5°C). An acceptable working potency standard qualification and maintenance program have been established. The reference standard for testing of future commercial JIVI potency is an in-house standard (Lot (b) (4) , designated as STD (b) (4)). This lot was assigned a potency value of (b) (4) against the WHO (b) (4) International Standard for factor VIII, Concentrate (b) (4) The method was adequately validated

for its intended use. The results of in-support testing for potency of the drug product were within specifications.

Stability
The proposed shelf-life for JIVI Final Drug Product (FDP) is 24 months from the date of manufacture when stored at 2-8 °C. Within this period, the FDP may be stored for up to 6 months at a temperature up to 25 °C, or up to 3 months up to (b) (4) The proposed expiry period of the JIVI Bulk Drug Substance (BDS) is (b) (4) from the date of manufacture when stored under the long-term storage condition of (b) (4) Within this period, JIVI BDS may be stored for up to (b) (4) at (b) (4)

b) CBER Lot Release

Under the provision described in 60 FR 63048-63049 publication (8 December 1995), routine lot-to-lot release by CBER is not required for JIVI because it is a well-characterized recombinant product. Thus, exemption of JIVI from CBER Lot Release is justified.

c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by OCBQ/CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of JIVI are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Manufacturing Facilities Table for JIVI Finished Packages

Name/address	FEI number	Inspection/ waiver	Results/ Justification
Drug Substance Manufacturing, Drug Product Manufacturing, Drug Product Release Testing, Drug Product Labeling, Primary and Secondary Packaging, Authorization of Finished Goods for Distribution Bayer Healthcare LLC	(b) (4)	Waived	ORA inspection (b) (4) VAI
Sterile Diluent Manufacturer, Release Testing (b) (4)	(b) (4)	Waived	ORA inspection (b) (4) VAI

Sterile Diluent QC release testing (b) (4)		Waived	Team Biologics (b) (4) VAI
Sterile Diluent QC release testing (b) (4)		Waived	CDER OPF (b) (4) VAI
Sterile Diluent manufacturer, primary packaging of sterile diluent, final release testing of sterile diluent Bayer	(b) (4)	Waived	ORA inspection (b) (4) VAI

VAI – Voluntary Action Indicated
NAI – No Action Indicated

The Office of Regulatory Affairs (ORA) conducted a surveillance inspection of Bayer Healthcare LLC from (b) (4). The inspection was classified as VAI and all inspectional 483 observations were resolved.

ORA conducted a surveillance inspection of (b) (4) The inspection was classified as VAI and all inspectional 483 observations were resolved. Team Biologics conducted a surveillance inspection of (b) (4). The inspection was classified as VAI and all inspectional 483 observations were resolved. A pre-approval inspection was performed by CDER/OPF of (b) (4) The inspection was classified as VAI and all inspectional 483 observations were resolved.

ORA conducted a pre-approval inspection for CDER of Bayer (b) (4). The inspection was classified as VAI and all inspectional 483 observations were resolved.

Container Closure System
The container closure system for JIVI consists of a glass vial, stopper, an aluminum seal, and plastic flip top. The FDP is filled into a 10-mL clear, colorless Type 1 silicone-coated glass vial. The vial is supplied by (b) (4). The stopper is made of gray bromobutyl rubber, silicone coated, and supplied by (b) (4). The overseal is a lacquered aluminum seal with plastic flip-off top. Container-closure integrity was demonstrated by (b) (4) testing, and all acceptance criteria in the study were met.

For administration of the drug product, there is a vial adapter that allows transfer of fluids between the diluent syringe and FDP vial as well as to the administration set(s). The vial adapter is manufactured by (b) (4), and is 510(k) cleared. There are three administration sets for drug delivery. The administration sets consist of a (b) (4) tube equipped with a cannula, Luer adapter, filter (optional), and wings. One administration set, (b) (4), which contains the integral filter is manufactured by (b) (4) The other administration sets, (b) (4) are both manufactured by (b) (4). The administration set, (b) (4), is supplied without an integral filter whereas administration set, (b) (4), is supplied with an integral filter. All three administration sets are 510(K) cleared.

The sWFI diluent packaged with the JIVI FDP is manufactured by (b) (4) and by Bayer (b) (4). For the diluent manufactured by (b) (4) the container for the 2.5-mL sWFI is a clear, colorless, borosilicate (b) (4) 3-mL syringe. The plunger stopper is of grey fluoropolymer-laminated, bromobutyl rubber. The tip-cap is a grey isoprene/ bromobutyl rubber stopper. For the diluent manufactured by Bayer (b) (4) the container for the 2.5-mL sWFI is a clear borosilicate glass, (b) (4) 5-mL syringe. The plunger stopper is of grey fluoropolymer-laminated, bromobutyl rubber. The tip-cap is a grey bromobutyl rubber stopper.

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31 (a). FDA concluded that this request is justified as the active moiety is not increased because the recombinant Factor VIII protein is catabolized during human metabolism and is not excreted by the patient. The sponsor also claimed that to their knowledge, no extraordinary circumstances exist.

e) Product Comparability

No changes were made in the manufacturing process, facilities and equipment between lots used in the Phase 3 clinical studies and conformance lots.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Multiple nonclinical studies in healthy rodents and nonrodents and in hemophilia A mice were conducted to evaluate the activity and safety profiles of JIVI (also termed BAY 94-9027 and KGN; PEG-FVIII), as well as the safety profile for BAY 1025662, which is the PEG-60-Maleimide-Cysteine linker moiety of JIVI.

JIVI

Single intravenous (IV) administration of JIVI (4-60 IU/kg) in hemophilia A (HemA) mice resulted in dose-dependent reduced bleeding times and blood loss similar to those generated in mice injected with Kogenate FS, following tail vein resection. Single IV administration of JIVI (50 IU/kg) in HemA dogs resulted in equivalent or better clotting

activity compared to dogs injected with Kogenate FS. This activity correlated with the longer half-life (T1/2) displayed in JIVI-injected dogs.

Repeat-dose IV toxicity studies in healthy adult male rats and rabbits administered JIVI every other day did not result in any significant adverse effects on the coagulation system or any organ systems. The NOAEL of JIVI was 2250 IU/kg/injection (37.5-fold higher than the maximum recommended prophylactic clinical dose level of JIVI).

A 52-week repeat-dose safety study in immune-deficient male rats to characterize the PEG tissue distribution/accumulation profile and any adverse findings following long-term repeat dosing with JIVI is ongoing. Rats were IV injected with up to 1200 IU/kg/injection of JIVI twice weekly for 26 weeks. Subgroups were sacrificed at 13 and 26 weeks. Remaining animals will be sacrificed at 52 weeks, following a 26-week recovery period. Based on the in-life data for all animals out to 26 weeks, and the histopathology data for the animals sacrificed at 13 and 26 weeks, no adverse clinical signs, clinical pathology, or organ histopathology findings were observed. In addition, there was no evidence of tissue vacuolation in any tissue examined and no presence of PEG in the brain (including the choroid plexus), kidney, spleen, or CSF.

Genotoxicity, carcinogenicity, and developmental and reproductive (DART) toxicity studies were not conducted with JIVI.

<u>BAY 1025662 (PEG-60-Mal-Cys component of JIVI)</u>
Single-dose and repeat-dose IV toxicity studies (up to 4 weeks of dosing) with BAY 1025662 in healthy adult male rats and rabbits and repeat-dose toxicity assessment in healthy neonatal male rats (twice weekly up to 4 weeks) were conducted at dose levels that were significantly higher than the amount of PEG (0.004 mg/kg) in a single administration of 60 IU/kg of JIVI. No significant adverse findings were seen. No immunohistochemical assessment of PEG was performed for the brain or any other organs, tissues, or body fluids. Cellular vacuolation was sporadically observed in some organs and tissues (testes, kidney, pancreas, parotid glands, choroid plexus, stomach and adrenal cortex) of control- and BAY 1025662-injected animals but was considered incidental by the pathologist. A series of in vitro and in vivo genotoxicity studies conducted with BAY 1025662 showed no evidence of mutagenicity.

5. CLINICAL PHARMACOLOGY

A pharmacokinetic (PK) study of JIVI was conducted in 14 males, between 18-65 years of age, who had severe hemophilia A. Single doses of JIVI, 25 IU/kg and 60 IU/kg were intravenously administered to subjects. The PK was also evaluated after dosing with 25 IU/kg given twice weekly and 60 IU/kg given once weekly for 8 weeks. The PK parameters were estimated based on plasma Factor VIII activity measured by the chromogenic and one-stage clotting assays. Blood samples for PK analysis were taken at time 0 (pre-infusion), 0.25, 0.5, 1, 3, 6, 8, 24, 48, 72, (96-144), and 168 hours following JIVI administration.

Based on the chromogenic assay, clearance and half-life of JIVI following 25 IU/kg and 60 IU/kg were 1.7 ± 0.4 mL/hour/kg and 19 ± 6 hours and 1.4 ± 0.4 mL/hour/kg and 19 ± 3 hours, respectively. Based on the clotting assay, clearance and half-life of JIVI following 25 IU/kg and 60 IU/kg were 1.7 ± 0.5 mL/hour/kg and 21 ± 13 hours and 1.4 ± 0.3 mL/hour/kg and 17 ± 1 hours, respectively. Multiple dosing of JIVI did not lead to accumulation of JIVI in plasma.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

i. The clinical development program included two studies to evaluate the safety and efficacy of JIVI to support a traditional approval. The two studies are:

1) Study 1: A study to evaluate the efficacy and safety of JIVI for on-demand, routine prophylaxis and perioperative management in previously treated patients (PTPs), adults and adolescents (≥12 years of age), with severe hemophilia A.

2) Study 2: A study to evaluate the efficacy and safety of JIVI for treatment of bleeding and routine prophylaxis in pediatric PTPs (<12 years of age) with severe hemophilia A

3) Although an agreement on the pediatric study plans (PSP) was not required at the time of the initiation of Studies 1 and 2, the sponsor did conduct a safety and efficacy study across all pediatric age groups.

Study 1 was a two-part, single-arm study in adults and adolescents.
Part A was designed to evaluate the efficacy of JIVI for the treatment of bleeding and for routine prophylaxis, and Part B was designed to evaluate the efficacy and safety of perioperative management of patients. In Part A, subjects received twice-a-week infusions of 25 IU/kg for 10 weeks for routine prophylaxis. Subjects who experienced 2 or more breakthrough joint or muscle bleeds spontaneously in the 10 week period were assigned to receive a higher dose: 30-40IU/kg twice a week. Subjects who had a lower rate of bleeding in the 10-week period were randomized 1:1 to one of two dosing frequencies, 45IU/kg (with allowable upper dose limit of 60 IU/kg) every 5 days or 60 IU/kg every 7 days. Subjects were evaluated for bleeding from Week 10 through Week 36. Thus, three doses and dosing frequencies were evaluated.

Part B was designed to evaluate the efficacy of JIVI in perioperative management. Subjects received a loading dose of 50 IU/kg or a dose determined by individual PK followed by 15-50 IU/kg to be repeated as indicated.

Efficacy Analysis Plan
The primary efficacy analysis was based on descriptive statistics in the ITT population. Response was defined as <9 total bleeds per year and conditional upon no changes to the dosing frequency. A 50% response would permit additional comparison of the

Annualized Bleeding Rates (ABRs) during the prophylactic phase for all three doses to on-demand therapy.

Results

Demographics
The age of enrolled adults ranged between 18-62 with a mean of 38 years. Thirteen subjects were between 12-17 years of age. The mean age of the pediatric study population was 14 years.

Efficacy
Part A (Results of on-demand and routine prophylaxis in adults and adolescents)

Twenty subjects received on-demand treatment and 114 subjects received prophylactic treatment of which 112 were evaluable for efficacy. The three dosing regimens evaluated under prophylaxis include 30 IU/kg twice per week, 45-60 IU/kg every 5 days and 60 IU/kg every 7 days. The results of the ABR for the on-demand treatment and routine prophylaxis that includes all three dosing regimens are provided below.

Table 1: ABR rates for On-demand and Prophylaxis (Weeks 0-36)

	ABR (n-132)	
Regimen	**On-demand (n=20)**	**Prophylaxis (n=112)**
Mean ± SD	28.83 ± 17.84	4.12 ± 4.77
Median (range)	24.13 (8.7-83.2)	2.82 (0-23.4)

Additional descriptive statistical assessment to evaluate the ABR rate for each of the three prophylactic regimens was performed, particularly since a risk-based approach based on bleeding risk in the first 10 weeks of treatment was used to select patients to receive a less frequent and/or lower-dose (less intense) regimen following the first 10 weeks of prophylaxis. Subjects who were selected to the two less intense dosing regimens represent a phenotypically different group than the subjects who continued on the twice weekly regimen. Therefore, assessment of ABRs in these groups were performed to assess whether less intense regimens (once every 5 days and once every 7 days) and twice weekly regimen had clinically acceptable ABRs. These results are described below:

Table 2: ABR Based on Types of Prophylactic Regimen (Weeks 10-36)

	ABR				
Regimen	**2x/week Failed[a] (n=13)**	**2x/week Forced[b] (n=11)**	**Every 5 days[c] (n=43)**	**Every 7 days[c] (n=43)**	**Total (n=110[d])**
Mean ± SD	7.24 ± 7.50	2.21±2.72	3.30±4.26	6.43±10.04	4.88 ± 7.49
Median (range)	4.11 (0-26.1)	1.93 (0-7.7)	1.93 (0-16.1)	3.85 (0-53.1)	2.09 (0-53.1)
Mean Dose per Infusion ± SD	38.9 ±2.9	31.5±3.5	45.3±3.2	56.8±4.4	47.7±9.2

[a] Failed: Subjects who remained on 30 IU/kg twice per week as the bleeding rates were > 2 spontaneous bleeding events during Weeks 0-10
[b] Forced: Subjects who remained on 30 IU/kg twice per week due to treatment caps in the once every 5-day regimen or 7-day regimen although they experienced ≤ 2 bleeding event during Weeks 0-10.
[c] Every 5 day or every 7-day regimen: Subjects who were randomized to receive either of these regimens based on having experienced ≤ 2 spontaneous bleeding events during Weeks 0-10.
[d] Two subjects dropped out prior to Week 10.

Part B (Peri-operative management of adults and adolescents)

Fourteen subjects underwent 17 major surgeries, 12 of which were orthopedic surgeries. One subject was an adolescent. Initial doses administered ranged between 2000-5000 IU, the median total dose per subject for major surgeries was 260.8 IU/kg. Hemostatic control was assessed as good or excellent in all cases. In the post-operative period, hemostatic control assessed at the post-surgical visit was good or excellent in all but three cases. In three cases, post-operative hemostasis was assessed as moderate. The results were considered acceptable to support a labelling indication for perioperative management.

Efficacy conclusions
The mean ABR observed in the "failed group" demonstrates that subjects who continued on the twice weekly regimen had substantially higher ABRs than subjects who were on the twice weekly "forced" group and the every 5-day regimen. These subjects with high ABR, under standard of care, would have individualized prophylaxis through escalation of doses or frequency to reduce the frequency of bleeding. Although subjects who were at a lower risk of bleeding were randomized to receive the once every 5- or 7-day regimen, the ABR in subjects who received the once every 7-day regimen was substantially higher (almost twice the mean ABR rate for subjects who were on every 5-day regimen). Given the high ABR rates with the twice-weekly regimen in the high-risk group (failed group) and the high ABR rate in the every 7-day group, the applicable dosing regimens will not be included in the label. Although the risk-based approach to selecting subjects in the study was based on a 10-week "test" regimen of 25 IU/kg twice weekly, the study did not evaluate such a regimen for prophylaxis purposes. Instead, these subjects were randomized after the 10-week test regimen to receive either a 30 IU/kg twice weekly or every 5- or 7-day regimen. Therefore, labelling recommendations for treatment are based primarily on the lowest frequency regimen, i.e., twice weekly regimen with the option of every 5-day regimen with acceptable bleeding rates in patients who continue to have low risk.

All adolescents were treated with prophylaxis and had a comparable ABR to those aged 18-34, but slightly higher compared to subjects over the age of 35. In the pediatric studies, the mean ABR was higher in the younger age group.

Bioresearch Monitoring
Bioresearch Monitoring (BIMO) inspections were conducted at one foreign and three domestic clinical study sites that participated in the conduct of Study 13024. The

inspections did not reveal any issues that impact the data submitted in this original Biologics License Application (BLA).

ii. Discussion of Post Marketing Requirements (PMR) and Post Marketing Commitments (PMC)

The safety issues in the indicated population have been sufficiently evaluated; therefore a PMR or PMC study is not recommended at this time. Issues regarding hypersensitivity and discontinuation of the JIVI with the development of hypersensitivity or loss of efficacy is included in the label and is sufficient to address the risks.

b) Pediatrics

The Applicant has completed efficacy and safety evaluation through pediatric studies across all age groups; 32 subjects 0-<6 years and 28 subjects 6-12 years. However, given the safety findings (see Section 6 below) related to hypersensitivity reactions, development of anti-PEG antibodies with loss of efficacy in pediatric subjects, an indication in the pediatric age group is not being pursued by the Applicant. Furthermore, the Limitations of Use section within the label will include information regarding the safety concerns in pediatric populations. No deferrals or waivers are being granted as the studies were already conducted.

c) Other Special Populations

In particular, no information is available as it relates to specific populations such as geriatric, pregnant, or nursing adults.

d) Pharmacovigilance

Bayer has proposed routine pharmacovigilance, inclusion in appropriate sections of the USPI, and an interventional post-marketing study (as required by the European Medicines Agency (EMA), but not required by FDA) to assess the safety and efficacy, for the following identified risks: development of Factor VIII inhibitors, hypersensitivity, and loss of efficacy (LoE) (due to anti-drug or anti-PEG antibodies). Bayer will also use follow-up questionnaires to assess LoE (due to Factor VIII inhibitors or anti-PEG antibodies), hypersensitivity, and renal impairment associated with the use of this product. Bayer has proposed a communication plan to inform healthcare providers regarding the indicated age for this product and the risk of hypersensitivity and development of LoE (due to anti-PEG antibodies) in individuals younger than 6 years of age. Bayer has proposed routine pharmacovigilance activities for the following missing information: long-term PEG-related adverse reactions, use in patients with severe hepatic or renal impairment, and use in patients older than 65 years of age.

7. SAFETY

One hundred and forty-eight (148) adult and adolescent (12-18 years) subjects and 73 subjects < 12 years of age were evaluable for safety. There were no deaths or

development of treatment-related FVIII inhibitors in adult, adolescent and pediatric previously treated patients. Two subjects who had low titer FVIII antibodies prior to surgery, had successful surgical outcomes with rising titers following exposure to the study drug. Due to the presence of pre-existing FVIII antibodies the change in antibody titer was not considered related to the study drug. Among the pediatric age groups (< 6 years and 6-12 years) no subject developed FVIII antibodies greater than the pre-specified threshold of 0.6 Bethesda Units (BU).

Hypersensitivity reactions

Of the adult, adolescent, and pediatric subjects, six subjects experienced hypersensitivity reactions. Two adult subjects (1.5%) developed hypersensitivity reactions; one subject developed a hypersensitivity reaction after the fourth dose and developed anti-drug and anti-PEG antibodies which were transient for up to one month. The second subject developed a hypersensitivity reaction after the first dose and did not develop anti-drug antibody or FVIII inhibitors. There were no drug-related serious adverse events other than the hypersensitivity reactions noted.

Of the subjects < 12 years of age, four subjects (5.5%) developed hypersensitivity reactions (three subjects were <6 years and one was 6 years of age). All three subjects <6 years of age developed anti-drug and anti-PEG antibodies. These three subjects also had pre-existing anti-PEG IgM antibodies and laboratory signs of loss of efficacy. The 6 year old subject did not develop any anti-drug antibodies.

Loss of Efficacy

There were 8 pediatric subjects who reported loss of efficacy (either detected clinically or via in-vivo recovery). Four subjects also had anti-PEG antibodies and developed neutralizing antibodies (NAB). Two subjects did not have laboratory findings of either of the anti-drug antibodies. Two subjects were negative for anti-PEG antibodies and unconfirmed neutralizing antibodies.

Drug Specific Antibodies (Anti-PEG and Anti-Drug (BAY94-9027))

The table below illustrates the increased number of Anti-Drug Antibodies (antibodies against the drug or its PEG moeity) detected in the population by age. Out of the samples tested, subjects in the pediatric population had a greater rate of Anti-Drug Antibodies. Most of the neutralizing antibodies occurred in subjects less than 6 years of age.

Table 3: Summary of Anti-Drug Antibodies, including Anti-PEG and Anti-BAY 94-9027

Type of antibody	**< 6 years (n=44)**	**6-12 years (n=29)**	**12-18 years (n=13)**	**>18 years (n=121)±**
Anti-PEG antibodies post treatment*	7/43	0/27	0/12	6/121
Ig M Anti-PEG antibody	4/32	0/22	1/10	1/98

Anti-BAY-94-9027	6/39	1/27	0/11	5/121
NAB BAY 94-9027**	8/24	0/3	0/0	2/15

*Four subjects > 12 years of age had baseline anti-PEG antibody and continued to be positive post-treatment and six developed anti-PEG antibodies post-exposure. Among the pediatric subjects < 12 years of age, 4 of 7 developed titers following study drug exposure and 3 with pre-existing titers had rising titers following exposure to the study drug.
±20 subjects had missing pre-treatment information but were negative for anti-PEG antibodies during treatment. Of these 20 subjects, 3 were negative for IgM anti-PEG antibody
**Neutralizing antibodies (NAB) included binding antibodies against the drug or its PEG moeity
NAB – neutralizing antibody

Summary of Safety Conclusions

No deaths or treatment-related FVIII inhibitors were observed in the safety evaluable pediatric, adolescent and adult subjects. In subjects with pre-existing FVIII antibodies, rising titers were observed particularly in the post-operative setting.

Hypersensitivity reactions were observed in 6 subjects; 4 subjects were < 12 years of age (three subjects <6 years and one 6 years of age). Three of the four pediatric subjects who experienced a hypersensitivity reaction had pre-existing anti-PEG IgM antibodies.

Anti-PEG antibodies were associated with hypersensitivity reactions. Of the 207 subjects evaluable for anti-PEG antibodies, 13 developed anti-PEG antibodies, of which 4 developed hypersensitivity reactions. Two (one adult subject and one pediatric subject) of the six subjects with hypersensitivity reactions did not develop anti-PEG antibodies. Development of anti-PEG antibodies was the highest in children < 6 years of age.

Loss of efficacy was associated with development of anti-drug antibodies in the pediatric subjects, but not in adults. In 23% of subjects in the age group <6 years of age, loss of drug effect due to anti-drug antibodies was observed.

In 7% of the subjects <6 years of age, loss of drug effect was combined with hypersensitivity reactions

Pre-clinical studies do not raise concerns related to PEG accumulation in the brain or renal tissues.

The safety profile in adults given the lower rate of (1.4%) of hypersensitivity reactions as compared to the rate in pediatric subjects less than 12 years of age (5.5%), is acceptable and risks should be communicated through the Warnings and Precautions Sections of the label. The risk of hypersensitivity in adults could be adequately mitigated by inclusion of information regarding increased risk of pre-existing anti-PEG antibodies, restricting the indication to adult and adolescent subjects, since the adult and adolescent subjects had lower risk than children less than 12 years. In addition, the risk

of hypersensitivity will be conveyed through the information in the prescribing information or label.

Due to the safety concerns in the pediatric age group, the recommendation is not to approve this product for use in patients less than 12 years of age. The risks of hypersensitivity and possible loss of efficacy outweigh the benefit for this age group. These risks will be addressed in the prescribing information.

8. ADVISORY COMMITTEE MEETING

An advisory committee meeting was not convened because the biologic is not the first in its class, the safety profile particularly with regard to long-term PEG accumulation associated with pre-clinical findings from a similar class of products is not a concern based on the pre-clinical findings for this product, the design of the study is similar to studies conducted to support other approved products, the review of the application did not raise significant safety concerns that could not be addressed through information in the label, consultative expertise was not required, and no public health concerns arose upon review of this file.

9. OTHER RELEVANT REGULATORY ISSUES

No major issues were identified, nor were there internal and external disagreements. Review of financial disclosure forms did not raise any concerns regarding study conduct.

10. LABELING

The proposed proprietary name, JIVI, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on September 11, 2017, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on October 17, 2017. The APLB found the prescribing information (PI) and package/container labels to be acceptable from a promotional and comprehension perspective.

i. The recommendation for approval of this BLA is for the following indication in adults and adolescents:

   1) Treatment and control of bleeding, routine prophylaxis to reduce the frequency of bleeding and peri-operative management.

   2) The initial recommended dose regimen will be 30-40 IU/kg twice weekly and may be adjusted to 45-60 IU/kg every 5 days, based on bleeding episodes. The Applicant's proposal included a dosing regimen at 6o IU/kg every (b) (4) days; however, the ABRs suggest that the risks of bleeding are substantial at this dose.

ii. Hypersensitivity and the potential loss of efficacy due to anti-PEG antibodies will be included in the Warnings and Precautions section.

iii. A medication guide is not required.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The CBER review committee recommends APPROVAL of this BLA for Antihemophilic Factor (Recombinant), PEGylated under the proprietary name JIVI. The manufacturing process for JIVI is considered adequately validated and controlled. Efficacy and safety clinical data for JIVI support a favorable benefit/risk determination for use in previously treated adults and adolescents (12 years of age and older) with hemophilia A (congenital Factor VIII deficiency) for:

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

b) Risk/ Benefit Assessment

The benefits of JIVI include:

1) On-demand JIVI is effective for treatment of and prevention of spontaneous or traumatic bleeding in patients with Hemophilia A

2) JIVI is effective in the perioperative setting for reduction of bleeding during surgery.

3) JIVI is effective in patients over (b) (4) years of age.

The risks of JIVI include:

1) Hypersensitivity reactions and development of anti-PEG antibodies which resulted in loss of efficacy in patients <12 years of age, as reported in the pediatric trial.

2) Although no reports of inhibitory antibodies to JIVI were noted in the studies, the risk of development of inhibitory antibodies is considered an expected adverse event.

The benefit-risk profile in patients 12 years of age and older is favorable. Therefore, the review team recommends approval for use in patients 12 years of age and older.

However, due to the risks of anti-PEG antibodies and hypersensitivity reactions, the risks outweigh the benefits in patients less than 12 years of age. Therefore, approval in this age group is not recommended.

c) Recommendation for Postmarketing Activities

No postmarketing requirement (PMR) or postmarketing commitment (PMC) studies are recommended.