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Application Type	Original Application
STN	125661/0
CBER Received Date	August 30, 2017
PDUFA Goal Date	August 30, 2018
Division / Office	DCEPT /OTAT
Priority Review	No
Reviewer Name(s)	Megha Kaushal, MD; Bindu George, MD
Review Completion Date / Stamped Date	8/23/2018
Supervisory Concurrence	Tejashri Purohit-Sheth, M.D.
Applicant	Bayer HealthCare LLC
Established Name	Antihemophilic Factor, PEGylated
(Proposed) Trade Name	Jivi
Pharmacologic Class	Recombinant, B-domain deleted
Formulation(s), including Adjuvants, etc	Intravenous Injection
Dosage Form(s) and Route(s) of Administration	Lyophilized Powder for Injectable Solution, Intravenous

Dosing Regimen	• On-demand treatment/Control of bleeding episodes: 20-40 IU/kg body weight for minor bleeds and 30-60 IU/kg body weight for moderate bleeds, and 60-100 IU/kg body weight for major bleeds; Perioperative management: Pre-operative dose of 30-60 IU/kg body weight for minor surgery, and 80-100 IU/kg body weight for major surgery. Routine Prophylaxis: The recommended initial regimen is 30-40 IU/kg twice weekly.
	• Based on bleeding episodes:
	  • The regimen may be adjusted to 45-60 IU/kg every 5 days.
	  • A regimen may be further individually adjusted to less or more frequent dosing.

Indication(s) and Intended Population(s)	Perioperative management of hemophilia (b) (4) subjects, {>12 years of age}; Control and prevention of bleeding episodes in hemophilia (b) (4) subjects, {>12 years of age}, Routine Prophylaxis, {>12 years of age}
Orphan Designated (Yes/No)	No

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GLOSSARY

ABR	Annualized Bleeding Rate
ADR	Adverse Drug Reaction
AE	Adverse Event
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
BU	Bethesda Unit
CMC	Chemistry, manufacturing, and controls
CI	Confidence Interval
eCTD	Electronic Common Technical Document
ED	Exposure Days
GCP	Good Clinical Practices
HS	Hypersensitivity
IU	International Units
LoE	Loss of Efficacy
PK	Pharmacokinetic
PMC	Postmarketing commitment
PMR	Postmarketing requirement
PREA	Pediatric Research Equity Act
PTP	Previously Treated Patient
PUP	Previously Untreated Patient
PVP	Pharmacovigilance Plan
rFVIII	Recombinant FVIII
SAE	Serious Adverse Event
T1/2	half-life
TEAE	treatment emergent adverse event

1. Executive Summary

Bayer submitted STN 125661 as an original biologics license application (BLA) submitted for the recombinant B- domain deleted (BDD) human coagulation factor VIII (rFVIII) product conjugated with a 60kDa branched polyethylene glycol (PEG), referred to as BAY 94-9027 with the proposed trade name JIVI. JIVI is a full length recombinant human factor FVIII produced in baby hamster kidney (BHK) cells and the active ingredient is claimed to be (b) (4) to the currently marketed product Kogenate FS.

Clinical trials that provided the evidence for safety and efficacy of JIVI were conducted under IND 14369. Data from the completed pharmacokinetic, adolescent and adult (Protocol 37583/Study 13024), pediatric (Protocol 38440/Study15912), and extension (Protocol 38453) studies were included for review. Studies 13024 and 15912 were the primary studies intended to support the marketing approval of JIVI under this BLA submission. These studies were reviewed to evaluate the efficacy and safety of JIVI for the following target indications for use in adults and adolescents (12 years and older) with Hemophilia A (HA):

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

The safety and efficacy of JIVI was evaluated in a total of 148 individual PTPs with severe Hemophilia A (factor VIII less than 1% of normal), who received at least one dose

of JIVI in the multicenter, open label clinical studies submitted in support of this application.

Study 1: (Protocol 37583/Study 13024): This study was a multicenter, open-label, uncontrolled study to evaluate the PK, safety, and efficacy of treatment with JIVI for prophylaxis and treatment of bleeds, and surgeries in previously-treated adults and adolescents (≥12 years of age) with severe hemophilia A (congenital FVIII deficiency).

The study was divided into two parts: Part A enrolled 134 subjects. One-hundred and twenty-six completed the study (including 13 subjects between 12 and 18 years of age) who were treated with JIVI for either on-demand (n = 18) or prophylactic treatment (n = 108). JIVI demonstrated efficacy with successfully treating bleeds with one or two infusions and decreasing the number of bleeds with prophylactic dosing. The three dosing regimens evaluated under prophylaxis included 30 IU/kg twice per week, 45-60 IU/kg every 5 days and 60 IU/kg every 7 days. 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). Moreover, prophylactic dosing with the every 7-day dosing regimen was not effective in 25% of subjects. ABR rates in subjects who were on the twice weekly “forced” group and the every 5-day regimen were comparable.

Part B enrolled 14 subjects who required major surgical procedures and who agreed to be treated with JIVI for surgical hemostasis. A total of 14 subjects underwent 17 major surgeries. In the extension study, 3 subjects completed 3 surgeries. Treatment with JIVI provided good or excellent hemostatic control.

Study 2 (Protocol 38453/Study13024): This study was an extension study of the main study and results were comparable to the main study. This study is ongoing.

Study 3 (Protocol 38440/Study15912): This study was a multicenter, open-label, uncontrolled study to evaluate the PK, safety, and efficacy of treatment with JIVI for prophylaxis and treatment of bleeds in previously-treated pediatric subjects (<12 years of age) with severe Hemophilia A.

Seventy-three subjects were enrolled who were treated with JIVI on different prophylactic regimens. Loss of drug effect and hypersensitivity reactions were noted in twelve subjects in this population. Ten of the 12 subjects had a PEG antibody. Hypersensitivity occurred in four pediatric subjects (5.5%) (three subjects <6 years and one subject 6 years of age). The rate of hypersensitivity in pediatric subjects was four times higher than the adult population. Loss of efficacy occurred in eight subjects (18%), all in subjects less than 6 years of age. Due to the unfavorable benefit risk assessment, JIVI is not recommended in those < 12 years of age.

This submission triggers PREA and the PERC meeting was held on April 18, 2018. There are no Post Marketing Commitments or Requirements.

Conclusion and Recommendation:
Based on the review of the submitted data, JIVI appears safe and efficacious in adults and adolescents over 12 years of age with Hemophilia A for the three indications being sought (on demand treatment and control of bleeding episodes; perioperative

management of bleeding; routine prophylaxis to reduce the frequency of bleeding episodes in in adults and children with Hemophilia A). The BLA is recommended for approval from the clinical perspective.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

All subjects were male. The median age in the adult/adolescent studies was 36 years of age. The median age in the pediatric study was 5 years of age. The predominant races represented in the study were white and Asian.

Table 1: Demographics and Baseline Characteristics

	<6 years	**6 to <12 years**	**12<18 years**	**>18 years**
N	44	29	13	121
Male	44	29	13	121
Race				
Not reported				9
White	37	28	7	81
Black	3	0	1	4
Asian	2	1	5	27
American Indian/Alaska Native	1	0	0	0
Native Hawaiian/Pacific Islander	1	0	0	0
Ethnicity				
Hispanic/Latino	5	0	1	5
Age				
Mean (SD)	3.5 (1.09)	8.55 (1.53)	14.1 (1.6)	38.3 (12)
Median [Min, Max]	3.5 [2,5]	9 [6,11]	13 [12,17]	37 [18,62]

Source: Adapted from BLA125661/0 Module 5.3.5.2 and 5.3.5.3 13024 Part A and Extension,15912 Protect Kids

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

1.2 Patient Experience Data

Table 2: Patient Experience Data Relevant to this Application

☒	The patient experience data that was submitted as part of the application include:		
	☒	Clinical outcome assessment (COA) data, such as	
		☒ Patient reported outcome (PRO)	
		☐ Observer reported outcome (ObsRO)	
		☐ Clinician reported outcome (ClinRO)	
		☐ Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	

	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
	☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review		
	☐	Input informed from participation in meetings with patient stakeholders	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.		

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

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

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

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

Currently, there are over ten licensed rFVIII products some of which are full-length FVIII products and others that are BDD products. These products are indicated for the control and prevention of bleeding episodes in adults and children (0-16 years) with HA, perioperative management in adults and children with HA, and routine prophylaxis to reduce the frequency of bleeding episodes and the risk of joint damage in children with HA. The following are the currently approved FVIII products.

Table 3: Approved FVIII Products

Product	Category	Full Length(FL)/ B Domain Deleted (BDD)	Cell Expression	Year approved
Recombinate	Recombinant	FL	CHO	1992
Kogenate	Recombinant	FL	BHK	1993
Refacto	Recombinant	BDD	CHO	2000
Advate	Recombinant Plasma/Albumin Free	FL	CHO	2003
Xyntha	Recombinant	BDD	CHO	2008
Novoeight	Recombinant	BDD	CHO	2013
Eloctate	Recombinant Fc Fusion Protein	BDD	HEK	2014
Obizur	Recombinant Porcine Sequence	BDD	BHK	2014
Nuwiq	Recombinant	BDD	HEK	2015
Adynovate	Recombinant 20kDA PEGylated	FL	CHO	2015
Afstyla	Recombinant Single Chain	BDD	CHO	2016
Kovaltry	Recombinant	FL	BHK	2016

JIVI is the first BDD, PEGYlated product.

2.3 Safety and Efficacy of Pharmacologically Related Products

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

The development of inhibitors decreases the efficacy of replacement therapy, necessitates FVIII dosage increases and/or the use of “bypass” agents, increases the risk of unmanageable bleeding and increases cost of treatment (by 3-5 fold)[2]. The incidence of inhibitor development is approximately 30% in severe disease and less in mild or moderate disease. The highest incidence is in previously untreated patients with

severe disease (reported incidence from 3-52%). Inhibitor development in previously treated patients who have not previously developed a FVIII inhibitor is less, reported as 0.9-4%. Potential risk factors for inhibitor development include genetic factors, such as the type of FVIII gene mutation, human leucocyte antigen (HLA) type, polymorphisms in immune regulatory regions, family history of inhibitors and ethnic background as well as immunologic environment during early treatment and high intensity of treatment (either peak acute treatment or high overall treatment frequency).

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

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

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

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

FDA had multiple interactions with the applicant throughout the IND and BLA process. In March 2009, a Type C Meeting was held. The main discussion included pre-clinical information on the adverse effects of PEGylation. FDA stated that it would be acceptable for Bayer to submit existing nonclinical safety pharmacology reports and data on target organ effects. FDA also agreed to support the surgical indication with 10 surgeries in at least 10 patients. The CMC development plan was also proposed at this meeting.

In November 2016, a Type C Meeting occurred with the main discussion on the clinical aspects of the pediatric study where a loss of efficacy was noted along with hypersensitivity. A discussion on PREA and not initiating a PUPs study was agreed upon.

A pre-BLA meeting was held in May 2017. CMC questions were clarified. Preclinical noted that the non-clinical testing program may not support filing of the BLA. Multiple comments were given regarding the chronic toxicology study. The applicant stated that they would limit the indications to adolescents and adults. We stated that the integrated safety summary should include data from all studies. An agreement was made to complete IgE evaluations in subjects who experienced hypersensitivity reactions, with the expectation that the results would be submitted with the 4-month safety update.

2.6 Other Relevant Background Information

This product contains a 60kDa branched PEG moiety and expected to be comparable to the 20kDa and 40 kDa linear moieties used with other rFVIII that have been approved.

An approved FIX product showed preclinical findings of PEG accumulation in the choroid plexus. The implications of PEG accumulation are unknown. A Blood Product Advisory Committee was held to gain input on the assessment regarding safety in the intended population, particularly in the pediatric and elderly populations, and in the setting of chronic administration of the pegylated FIX product. FDA asked whether monitoring, specifically for neurocognitive function, should be done for the safety of the intended patient population. In addition, FDA asked whether additional data are necessary to evaluate the issue of PEG accumulation in the choroid plexus. Based on their discussion, the majority of the AC members suggested that a post-marketing study be conducted to assess neurologic and neurocognitive parameters in a

standardized manner. All of the committee members agreed that short-term use (on demand treatment and perioperative use) of the study drug was not concerning. The committee members agreed that premarketing approval studies would be useful; and, post-marketing studies may be sufficient to collect more safety data with respect to neurocognitive function in patients.

JIVI, a pegylated product, did not show any preclinical findings of PEG accumulation. An ongoing 52-week toxicology study in immune-deficient (b) (4) nude male rats with a 26-week intravenous dosing period and a 26-week recovery period was requested, which showed no evidence of accumulation of the PEG moiety. PEG accumulation does not appear to be a concern with this product.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

3.2 Compliance With Good Clinical Practices And Submission Integrity

CBER Bioresearch Monitoring issued inspection assignments for four study sites.

Table 4: BIMO Inspection Sites

Site #	Number of subjects	Location	Inspection Status
14002	10	Penn State Health Milton S. Hershey Medical Center, Hershey, Pennsylvania	NAI
14013	3	SUNY Upstate Medical University Syracuse, New York	NAI
14024	3	University of California -Davis Sacramento, California	NAI
68001	6	Singapore General Hospital, Singapore	NAI

NAI = No Action Indicated

The four sites were selected for inspection based on number of subjects enrolled at the sites, and no concerns regarding data integrity were raised. No significant regulatory violations were noted and a Form FDA 483 was not issued at any site. All for inspections were classified as NAI. Please refer to the BIMO review memo for full details.

3.3 Financial Disclosures

Complete financial disclosures were provided for the studies and reviewed. No significant financial interests or conflicts were identified that could potentially bias the conduct of the study. A complete list of clinical investigators was provided, and four investigators had disclosable financial interests/arrangements and submitted Form FDA 3455. These investigators did not receive significant payments or clinical training awards

from Bayer. The details of the disclosable arrangements were provided along with a description of the steps taken to minimize potential bias.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

JIVI is a recombinant, beta domain deleted human factor VIII with a 60kDa polyethylene glycol moiety. The active protein (or starting molecule), prior to conjugation is a recombinant B-domain deleted human coagulation Factor VIII (BDD rFVIII) produced by recombinant DNA technology in Baby Hamster Kidney (BHK) cells. The conjugated protein is prepared without the addition of any human or animal derived protein in the cell culture process, purification, site-specific pegylation or final formulation.

There were no significant issues relating to CMC. Please refer to the CMC memo for full details.

4.2 Assay Validation

Required validation of applicable methods and release specifications have been completed. Please refer to the CMC review memo for complete details.

4.3 Nonclinical Pharmacology/Toxicology

Please refer to the Pharmacology/Toxicology review memo for complete details.

As PEG accumulation in the choroid plexus and other organs was a concern raised with another PEG-conjugated rIX product, a 26-week intravenous toxicology study in immune-deficient (b) (4) nude male rats, with a 26-week recovery interval was initiated. This study was requested by FDA in the May 31, 2017 Type B pre-BLA meeting. The applicant submitted an audited interim report containing all in-life data from all study animals and post-mortem data (including histopathology) from the animals sacrificed at the weeks 13 and 26 time points, in an amendment to the BLA. No adverse effects were observed in immune-deficient rats intraveneously injected with JIVI (40-1200 IU/kg/injection), twice weekly for 26 weeks. No evidence of accumulation of the PEG moiety component of JIVI was detected by immunohistochemical staining in the brain (including the choroid plexus), spleen, or kidneys in animals sacrificed at 13 and 26 weeks. A final audited report (to also include the 26-week recovery data) is to be submitted in the first quarter of 2019.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

JIVI, a site-specifically PEGylated recombinant antihemophilic factor, temporarily replaces the missing coagulation Factor VIII. The site-specific PEGylation in the A3 domain reduces binding to the physiological Factor VIII clearance receptors.

4.4.2 Human Pharmacodynamics (PD)

The aPTT is prolonged in people with hemophilia A. Determination of aPTT is based on a conventional in vitro assay for biological activity of Factor VIII. Treatment with JIVI normalizes the aPTT similar to that achieved with plasma-derived Factor VIII. The

administration of JIVI increases plasma levels of Factor VIII and can temporarily correct the coagulation defect in hemophilia A patients.

4.4.3 Human Pharmacokinetics (PK)

Incremental recovery and trough levels were assessed in all subjects at the baseline visit and at various intervals. The PK parameters were based on plasma Factor VIII activity measured by the chromogenic and one-stage clotting assays.

Please refer to the Clinical Pharmacology review memo for complete details.

4.5 Statistical

The statistical reviewer verified that the primary study endpoint analyses cited by the applicant were supported by the submitted data. There were three bleeding events that were not captured in the data submitted by the applicant. These bleeding events were included in the efficacy analysis, label and in the SBRA.

4.6 Pharmacovigilance

Bayer has proposed 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 exposure days, as required by EMA, but not FDA. This study will 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.

Please see the OBE review for further details.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

Clinical trials that provided the evidence for safety and efficacy of JIVI were conducted under IND 14369. Data from the completed adult (Protocol 13024- PH37583), pediatric (Protocol 15912-PH38440), and extension (Protocol 13024- PH38453) trials were included for review to evaluate the efficacy and safety of JIVI.

Review Responsibilities:
Product and Chairperson: Zuben Sauna
Clinical: Megha Kaushal, Bindu George
Statistician: Lin Huo
ClinPharm: Iftekhar Mahmood
Pharm/Tox: Sandhya Sanduja

APLB: Kristine Khuc
BIMO: Bhanu Kannan
DMPQ: Lori Peters
OBE: Graca Dores
RPM: Candace Jarvis

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

Documents pertinent to this review were provided in BLA125661/0 and IND 14369, including the clinical summary, overview, and clinical study reports.

5.3 Table of Studies/Clinical Trials

Table 5: Clinical Studies

PK Efficacy and safety Phase 2/3	**PROTECT VIII (13024)**	**A phase II/III, multicenter, partially randomized, open label trial investigating safety and efficacy of on-demand and prophylactic treatment with BAY 94-9027 in severe hemophilia A Comprises: PROTECT VIII Main study (Part A and B) PROTECT VIII Interim Extension (Part A and B), as of 9 Jan 2015**	**Completed (Extension ongoing)**
PK Efficacy and safety Phase 3	**PROTECT Kids (15912)**	**A multi-center, phase III, non-controlled, open-label trial to evaluate the pharmacokinetics, safety, and efficacy of BAY 94-9027 for prophylaxis and treatment of bleeding in previously treated children (age <12 years) with severe hemophilia A Comprises: PROTECT Kids Main study PROTECT Kids Part 2**	**Completed (Extension ongoing)**

Source: Adapted from BLA125661/0 5.2 Tabular Listing of all Clinical Studies pages 2 and 4

5.4 Consultations

No consultants were used during the review of this BLA.

5.4.1 Advisory Committee Meeting (if applicable)

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 similar class of products are not a concern based on review of the pre-clinical studies in support of the BLA, the design of the clinical 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.

5.4.2 External Consults/Collaborations

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

5.5 Literature Reviewed (if applicable)

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

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: Protocol 37583/Study 13024

Clinical Trials Identifier: NCT01333111
Initiated: April 29, 2011 Trial Completed: April 2, 2013

A Phase II/IIII, multicenter, partially randomized, open label trial investigating safety and efficacy of on-demand and prophylactic treatment with JIVI in Severe Hemophilia A

6.1.1 Objectives (Primary, Secondary, etc)

Part A: The primary objective was to assess the efficacy of JIVI in prevention and treatment of bleeding using different infusion schedules.

The secondary objectives were:

- To evaluate the subject's assessment of response to treatment
- To demonstrate the safety and tolerability of the study drug when used in both the on demand and prophylaxis settings
- To assess frequency of inhibitor development
- To assess PK and incremental recovery following administration of the study drug
- Assess treatment satisfaction with the study drug and its impact on quality-of-life, work productivity and pain as reported by the subjects.

Part A Extension: The primary objective was to assess the long term safety of the study drug over at least 100 accumulated exposure days (ED).
Please refer below to clinical study #2 for review of the ongoing extension study.

Part B: The primary objective was to assess the safety and efficacy of JIVI in the prevention of bleeding during major surgical procedures.

6.1.2 Design Overview

Part A was a multicenter, multinational, partially randomized, open label trial evaluating the PK, safety, and efficacy of JIVI with different dosing frequencies in both the prophylactic and on-demand treatment of bleeding in adults and adolescents with severe hemophilia A.

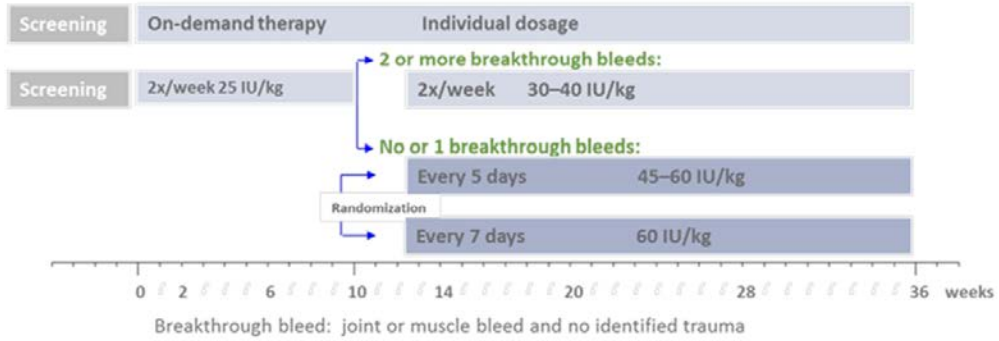
Enrolled subjects were included in the study if they were between 12 and 65 years of age with severe hemophilia A who had a documented history of at least 150 exposure days (ED) with any FVIII product. The total duration of the main trial was approximately 36 weeks to ensure that at least 50 subjects across the different treatment groups had 50 ED.
Subjects completing Part A of the main trial were offered participation in an optional extension for a minimum of 6 months and at least 100 total ED.

The study of on-demand and prophylactic treatment was divided into two treatment groups. Subjects were asked to identify their preferred treatment when signing consent. Subjects who were not treated with routine prophylaxis could enter the on-demand arm. Subjects would use the study drug as needed for acute bleeding episodes with a maximum dose of 60 IU/kg.

Subjects in the prophylaxis arm started treatment with twice weekly (2x/week) infusions at a dose of 25 IU/kg. At the Week 10 clinical assessment, subjects were randomized to a less frequent infusion treatment arm based on eligibility.

Subjects who were determined to be at high risk of repeated bleeding, defined as having experienced 2 or more breakthrough (spontaneous, no identified trauma) joint and/or muscle bleeds during the first 10 weeks of treatment, were to remain in the 2x/week treatment arm. These subjects were to increase the dose administered to 30-40 IU/kg to achieve improved bleeding control. The remaining subjects, those who had fewer than 2 breakthrough bleeds, were to be randomized 1:1 and assigned to a less frequent dosing arm (every 5 days or every 7 days). Subjects randomized to the every 5 days treatment arm were to begin treatment with a dose of 45 IU/kg infused every 5 days. Subjects on the every 7 days arm were to be treated with a fixed dose of 60 IU/kg. After the randomization had closed, the remaining subjects had to continue treatment in 2x/week arm. See below at Figure **1** for the Study design, as described above.

Figure 1: Part A Study Design



Source: Adapted from BLA125661/0 CSR PH-37583 Figure 7-1 page 31/1305

Part B was an open label, non-controlled, single arm study for subjects who required major surgery. Part B was open to all subjects participating in Part A and to individuals with severe hemophilia A not otherwise enrolled in this clinical study who met the same inclusion and exclusion criteria as required in Part A. Part B was not to be opened to enrollment until at least 20 bleeding events from Part A had been assessed to ensure the hemostatic activity of the investigational product.

Major surgery was defined as any surgical or invasive procedure (elective or emergent) in which the overall bleeding risk may have been excessive, would have required a general anesthetic in an individual without a bleeding disorder, penetrated or exposed a major body cavity, could have resulted in substantial impairment of physical or physiological functions, or required special anatomic knowledge or manipulative skill (e.g., tonsillectomy, laparotomy, thoracotomy, joint replacement).

The frequency of breakthrough bleeds in each of the prophylaxis arms was to be compared with the frequency of bleeds in the on-demand arm and to the frequency of breakthrough bleeds in historic prophylaxis trials with full-length rFVIII-FS. It was agreed in scientific advice with regulatory authorities that a controlled comparator arm was not necessary for this study.

6.1.3 Population

The key inclusion criteria were as follows:

1. Male; 12 to 65 years of age (or male 18 to 65 years of age in countries where enrollment of minors was not permitted)
2. Subjects with severe hemophilia A (baseline FVIII activity FVIII:C <1%) determined by measurement at the time of screening or from reliable prior documentation (eg, measurement in other clinical trials, result from approved clinical laboratory)
3. Previously treated with FVIII concentrate(s) (plasma derived or recombinant) for a minimum of 150 ED

Key exclusion criteria were as follows:

1. Current evidence of inhibitor to FVIII with a titer ≥ 0.6 BU/mL, measured by the (b) (4) Bethesda assay at the time of screening (central laboratory)
2. History of inhibitor to FVIII with a titer ≥ 0.6 BU, or clinical history suggestive of inhibitor requiring modification of treatment. Subjects with a maximum historical titer of 1.0 BU on a single measurement but with at least 3 subsequent successive negative results (< 0.6 BU) thereafter, were eligible for study inclusion
3. Any other inherited or acquired bleeding disorder in addition to Hemophilia A

Subjects were required to be withdrawn from the study for the following reasons:

-Development of an inhibitory antibody to FVIII or the study drug that neutralized activity sufficiently to interfere with effective treatment or required use of a bypassing agent to treat bleeds
- Failure to comply with scheduled appointments for study-related testing or with EPD data entry to an extent that compromised collection of critical data
- Significant concurrent illness or deterioration in the subject's condition, including laboratory values that the investigator deemed to be incompatible with the subject's continued safe participation in the study

6.1.4 Study Treatments or Agents Mandated by the Protocol

The following investigational medicinal product was used in the trial: JIVI
The investigational product was supplied as a lyophilized powder in glass vials. Study vials contained 250 IU, 500 IU, 1000 IU, or 3000 IU of FVIII activity.

6.1.5 Directions for Use

Subjects enrolled in a prophylaxis arm received 25-60 IU/kg with a maximum of 6000 IU.

For all subjects in the trial, the dose levels of JIVI for treatment of a mild or moderate bleeding episodes were treated based on the severity of the bleed. The maximum dose was 60 IU/kg.

In the surgery trial, subjects were given a loading dose of 50 IU/kg (or as determined by individual PK) given < 60 min before start of procedure; a 15 to 50 IU/kg (rounded to full vial) repeated as indicated.

6.1.6 Sites and Centers

A total of 134 subjects received treatment in Part A of the study at 57 centers in 19 countries, which included Austria, Belgium, Canada, Colombia, Germany, Denmark, France, United Kingdom, Israel, Italy, Japan, South Korea, Netherlands, Norway, Poland, Singapore, Turkey, Taiwan, and the United States.

6.1.7 Surveillance/Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors contacted the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. The sponsor/designee monitored the site activity to verify that the:

- Data were authentic, accurate and complete
- Safety and rights of subjects were being protected
- Study was conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements were met.

At the screening visit (before any study procedure was performed) a signed and dated written informed consent document was to be obtained from the subject. The subjects were to receive a detailed explanation of the study from the investigator or his/her delegate. Once written informed consent was obtained, the Investigator was to perform the specific procedures and assessments.

For guidance to the subject or their caregivers, the following definitions for response to treatment were provided:

Excellent: Abrupt pain relief and/or improvement in signs of bleeding with no additional infusion administered
Good: Definite pain relief and/or improvement in signs of bleeding, but possibly requiring more than one infusion for complete resolution
Moderate: Probable or slight improvement, with at least one additional infusion for

complete resolution
Poor: No improvement or condition worsened.

6.1.8 Endpoints and Criteria for Study Success

Treatment of bleeds:
-Annualized number of bleeds in the on-demand treatment arm
-Description of bleeding per location and frequency of total bleeds (spontaneous and trauma), joint bleeds, trauma, spontaneous bleeds and all bleeds
-Number of infusions required to control a bleed
-Subject or investigator assessment of response to treatment of a bleed, as excellent, good, moderate, poor

Table 6: Perioperative Rating Scale

Treatment	Rating	Definition
Intra-operative	Excellent	Blood loss less than expected
	Good	Blood loss as expected
	Moderate	Blood loss more than expected
	Poor	Uncontrolled bleeding
Post-surgical	Excellent	As good or better than other FVIII concentrates
	Good	At least as good as other FVIII concentrates
	Moderate	Less than optimal for the type of procedure, but no need to change therapeutic regimen
	Poor	Breakthrough bleeding due to inadequate therapeutic response, change in therapeutic regimen required

Source: Adapted from BLA125661/0 CSR PH-37583 Table 7-6 page 71/1305

6.1.9 Statistical Considerations & Statistical Analysis Plan

Efficacy data were summarized for all subjects in the ITT population. In the protocol, it is stated that the efficacy objective will be achieved if at least 50% of subjects respond. A responder was defined as a subject with less than 9 total bleeds per year who did not increase his dosing frequency or drop out.

6.1.10 Study Population and Disposition

A total of 15 subjects who received on-demand therapy and 65 subjects who received prophylactic therapy had minor protocol deviations. A total of twelve subjects had a deviation described as “important”. The important deviations noted during this study include administration of doses higher than 6000 IU per infusion and use of expired study medication.
There were no major protocol deviations during the study. There were no safety concerns reported by the applicant in association with these deviations.

There were 3 subjects in Part A with doses higher than the maximum dose per infusion of 6000 IU. There were also 10 subjects who had 14 infusions with expired study medication. Neither of these deviations related to any AE or any lack of efficacy.

6.1.10.1 Populations Enrolled/Analyzed

This trial enrolled subjects with severe hemophilia A aged 12 to 65 years. There were 13 subjects between the ages of 12-17 years.

6.1.10.1.1 Demographics

Table 7: Demographics

	Total
Number of Subjects	134
Age at baseline(years) Mean (SD)	35.9 (13.5)
Median	35.0
Min; Max	12; 62
Ethnicity	
Hispanic or Latino (%)	6 (4.5%)
Race (%)	
Asian	32 (23.9)
Black	5 (3.7)
White	88 (65.7)
Not Reported	9 (6.7)

Source: Adapted from BLA125661/0 CSR PH-37583 Table 8-3 page 92/1305

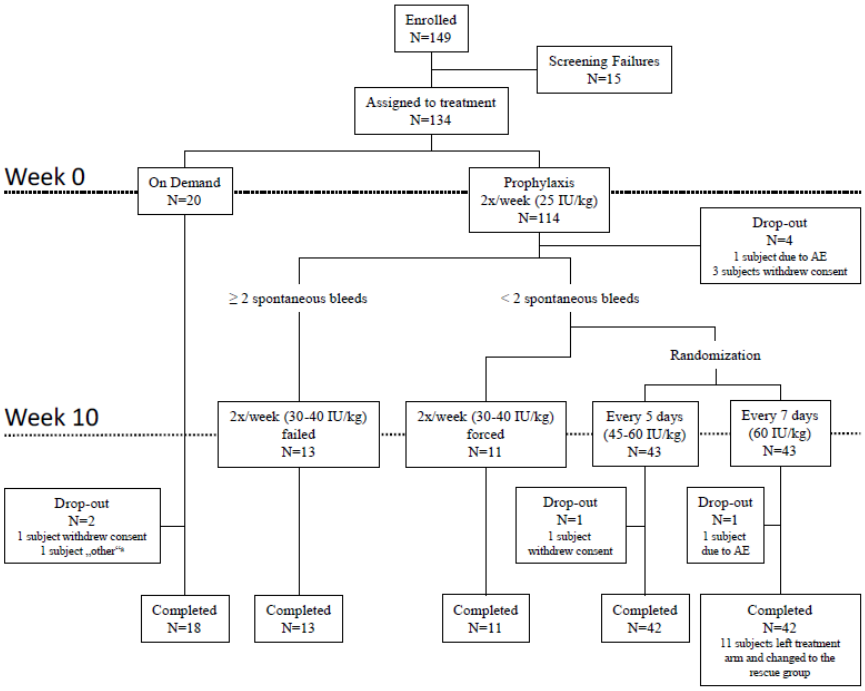
The majority of subjects were white (88 subjects, 65.7%) and, per protocol, all (100%) were male. Subjects had a mean age of 35.9 years (range 12 to 62 years).

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Severe Hemophilia A was confirmed for all subjects at screening. A total of 98 subjects had a target joint upon study entry.

6.1.10.1.3 Subject Disposition

Figure 2: Disposition



Source: Adapted from BLA125661/0 CSR PH-37583 Figure 8-1 page 86/1305
Failed group: Those subjects who experienced ≥ 2 spontaneous bleeds from Weeks 1-10.
Forced group: Those subjects who experienced 1 or no spontaneous bleeds from Weeks 1-10, who were otherwise eligible to be randomized to every 5 or 7 day regimens, but were forced to continue treatment twice weekly from Wks 10-36 since the cohorts with the 5 or 7 day regimens were capped to enrollment.

There were 132 subjects evaluable for efficacy. The primary assessment of efficacy was based on 110 subjects who received JIVI for routine prophylaxis during Weeks 10–36 of Part A. Of these, 107 subjects participated in the optional extension phase.

Reviewer Comment: One hundred and twenty six subjects completed the study for the full time period of 36 weeks. Of note, 25% of the every 7-day regimen subjects were "rescued" to a lower dose (eight subjects changed to every 5 days and 3 changed to 2x/week infusion). No subject discontinued from the every 5-day treatment arm, but 16% did have their dose increased due to bleeding.

One subject denoted as "other" dropped out in the on-demand group due to non-adherence to the study protocol and was not related to an AE.

For subjects who received prophylaxis treatment in Part A, most (91 subjects) were on a prior prophylactic treatment regimen. Out of the 134 subjects, 98 subjects (73.1%) had a target joint. Thirty-seven subjects (27.6%) had one target joint. Twenty-seven subjects had two target joints (20.1%), 17 subjects had three target joints (12.7%) and 17 subjects had four or more target joints (12.7%). Most subjects (67.9%) had been on prior FVIII treatment with prophylaxis.

The mean ± standard deviation (SD) number of bleeds in the previous 12 months was 15.3 ± 18.6. The mean ± SD number of joint bleeds in the previous 12 months was 11.5 ± 16.5.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary objective was to assess the efficacy of JIVI in prevention and treatment of bleeding at different infusion schedules. Annualized Number of Bleeds/Annualized Bleeding Rate (ABR) was used for this evaluation.

There were 20 subjects who received on-demand therapy and had a total of 388 bleeds. There were 112 subjects who received prophylaxis therapy and had a total of 317 bleeds; however, only 110 subjects were eligible for the primary efficacy assessment due to two subjects early discontinuation from the study. The mean (SD) total dose per kilogram per infusion was 35.5 (9.4) IU/kg/infusion for the on demand group and 38.6 (5.3) IU/kg/infusion for the prophylaxis group.

Reviewer Comment: There were three bleeding events that were detected after database closure, which were reported by the applicant. Therefore, the total number of bleeds is 388 bleeding episodes, and not the 386 bleeds reported by the applicant for those in the on-demand group in the clinical study report. There were a total of 317 bleeds in the prophylaxis group, and not 316 bleeds as reported by the applicant in the clinical study report. This bleed in the prophylaxis subject occurred in the first 10 weeks. Minimal information was provided on the three additional bleeds. These additional bleeds will have minimal changes in the mean and median ABRs. This update will be reflected in the label.

The median number of bleeds was 15.5 bleeds (range 5-59) over 36 weeks in the on-demand group. The median ABR was 23.42 and the mean ABR was 28.60 ± 17.97. The ABR in the prophylaxis group was lower compared to the on-demand group as shown below. There were 37 subjects (33%) who received prophylaxis treatment across all regimens who had no bleeding.

Table 8: Summary of Bleeds for Weeks 0-36

	On-demand	Prophylaxis
N	20	110
# of total bleeds	388	317
Mean ± SD*	19.3 ± 13.1	2.8 ± 3.4
Median (range)*	15.5 (5-59)	2.0 (0-17)
ABR		
Mean ± SD*	28.83 ± 17.84	4.12 ± 4.77
Median (range)*	24.13 (8.7-83.2)	2.82 (0-23.4)

*These numbers reflect the three additional bleeds
Source: Reviewer

Reviewer Comment: The ABR is expected to be lower in those who receive prophylaxis versus those subjects who receive on demand therapy. The ABR for the prophylaxis group across all regimens is consistent with other FVIII products.

After 10 weeks, bleeding was evaluated for subjects with a dose of 25 IU/kg who received the drug 2x/week. Thirteen out of the 110 subjects were identified as high bleeders (failed group). The remainder of the subjects had a median of 0 total bleeds and qualified for randomization to either the every 5-day or 7-day treatment regimen. There were 86 subjects who qualified for randomization to every 5 days or every 7 days.

Eleven subjects who qualified for randomization continued the 2x/week treatment due to capping for the other treatment arms.

Reviewer Comment: Subjects with worse phenotypes with respect to bleeding were placed on a regimen that would give them frequent dosing with a higher dose than the first 10 weeks and were noted as the "Failed" group. Those with similar bleeding characteristics were randomized to higher dosing at less frequent intervals. It is unclear whether these individuals are truly phenotypically worse and what variables may have contributed to the phenotypically worse subjects in this short period of 10 weeks.

The following is a Summary of Bleeds in Weeks 10-36

Table 9: Routine Prophylaxis- Bleeds in Weeks 10-36

	2x/week Failed	2x/week Forced	Every 5 days	Every 7 days	Total
N	13	11	43	43	110
# of total bleeds	47	13	70	76	206
Mean ± SD	3.6±3.8	1.2±1.5	1.6±2.1	1.8±2.0	1.9 ± 2.3
Median (range)	2.0 (0-13)	1.0 (0-4)	1.0 (0-8)	1.0 (0-7)	1.0 (0-13)
Mean Dose per Infusion	38.9 ±2.9	31.5±3.85	45.3±3.2	56.8±4.4	47.7±9.2
ABR					
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	38.9 ±2.9	31.5±3.85	45.3±3.2	56.8±4.4	47.7±9.2

Source: Adapted from BLA125661/0 CSR PH-37583 Table 9-3 page 100/1305

In the subjects identified as bleeders who remained in the twice weekly treatment, their mean dose increased from 28.6 IU/kg/infusion to 38.9 IU/kg/infusion. At this dose, they experienced improvement in bleeding with a median ABR that decreased from 17.4 (in the first 10 weeks) to 4.1 in weeks 10-36.

In the 11 subjects (forced group) who were not randomized and not considered high risk bleeders during the first 10 weeks at a dose of 25 IU/kg, received a mean dose of 31.5 IU/kg/infusion. Their median ABR increased from 0 to 1.9 despite higher doses. This observation may be due to the longer duration of follow up in Weeks 10-36.

Thirteen subjects (12%) who failed the 25 IU/kg twice weekly regimen with a mean ABR of 19, then received a higher median dose of 38.9 IU/kg, and despite the higher dose, continued to have a clinically unacceptable ABR rate of 7.24 (Table 6). Despite the higher ABR in the failed group, the ABR observed in the forced group is clinically meaningful and confirms that the dose of 30-40 IU/kg is an alternate regimen for patients who were at a low risk of bleeding.

The 43 subjects who were randomized to every 5 days received a mean dose of 45.3 IU/kg/infusion had a mean ABR of 3.30, which is an acceptable ABR. In the subjects that were randomized to every 7 days, subjects received a mean dose of 56.8 IU/kg/infusion. Eleven subjects dropped out of this treatment arm after experiencing a bleed (eight subjects changed to every 5 days and 3 changed to 2x/week infusion). Of the 11 drop

outs from the 7-day regimen, eight subjects received doses that ranged from 45-60 IU/kg every 5 days and three subjects received doses that ranged from 30-40 IU/kg twice weekly. The mean ABR in the 7-day regimen group was 6.43 and is clinically unacceptable.

Reviewer Comment: All the ABRs increased from weeks 10-36 as compared to the first 10 weeks which could be due to the short duration of time that subjects were exposed to the study drug in the first ten weeks. The 26 weeks thereafter would reflect a more accurate ABR for that study population. Those in the failed group continued to have high mean ABRs (7.24). Those on the twice weekly dose who failed the 25/IU/kg regimen and subsequently received 30-40 IU/kg twice weekly, had clinically unacceptable ABR rates of 7.24 suggesting that these patients may require additional dose titrations to higher and/or more frequent doses as with individualized prophylaxis. Those who had lower bleeding rates in the 10 week trial period who were either switched to every 5 day dosing or switched to the forced 30-40 IU/kg twice weekly had ABRs consistent with other approved FVIII products. Thus, a starting dose of 30-40 IU/kg twice weekly for a period of 10 weeks could in patients at lower risk of bleeding (1 or less bleeds) provide the option to allow extended dosing at 30-40 IU/kg twice weekly (same dose) or to switch to a less frequent dose of 45-60 IU/kg every 5 days without substantial risk of breakthrough bleeding. The recommendation should include individualized prophylaxis for those patients who experience 2 or more bleeds in the 10 week period following treatment with the 30-40 IU/kg dose. The recommendation for the starting dose, individualized prophylaxis and parameter to switch to the 5 day regimen will be included in the label.

Those subjects with every 7 day dosing had a high mean ABR. Moreover, there were eleven out of 43 subjects (25.6%) who dropped out after experiencing bleeding episodes for those dosed in the every 7-day prophylaxis regimen. Given the number of subjects who required rescue treatment, a mean ABR rate that places subjects at substantial risk of bleeding while on a prophylactic regimen, inability to identify characteristics of subjects who are likely to benefit from an every 7-day regimen and in the absence of pre-specified eligibility criteria to define this group of subjects (who are at low risk of bleeding with a 7-day regimen), the reviewer recommends that this dosing not be considered a viable option for patients and removed from the label. Individualized prophylaxis at prescriber discretion to less frequent dosing regimens could be considered for those patients who have control of bleeding on the 5-day dosing regimen, given that 75% of patients had adequate reduction in bleeding. These recommendations will be included in the label.

The median ABR for spontaneous bleeds was 14.29 bleeds/year in the on-demand group and 0 in the prophylaxis group. The mean (SD) ABR for spontaneous bleeds was 17.19 (13.19) bleeds/year in the on-demand group and 3.41(6.72) in the prophylaxis group. The median ABR for traumatic bleeds was 9.09 bleeds/year in the on-demand group and 0 in the prophylaxis group. The mean (SD) ABR for traumatic bleeds was 11.48 (10.96) bleeds/year in the on-demand group and 1.47 (3.12) in the prophylaxis group. Most of the bleeds occurred in the joints (152/206; 73.8%) and 72 of these were in a target joint. Of the 206 bleeding events, 205 were characterized by severity of the bleeds and were as follows: Mild (99; 48.1%), Moderate (96; 46.6%), and Severe (10; 4.9%).

Table 10: Number of Infusions Required to Treat Bleeds, Weeks 0-36

	On-Demand	Prophylaxis	Total
N (number of subjects)	20	112	132
Number of Infusions to control bleed			
1 infusion	309*	263*	572*
2 infusions	45	22	67
≥ 3 infusions	34	32	66

Source: Clinical reviewer
*The additional three bleeds not included in the Applicant's analyses are reflected above. They will be included in the label.

A total of 569 bleeds (81.1%) were treated with one infusion and 67 bleeds (9.5%) were treated with two infusions. The adequacy of hemostasis was judged to be excellent/good in 508/702 (72%) bleeds.

Reviewer Comment: This clinical reviewer agrees with the assessment above regarding the adequacy of hemostasis. The adequacy of hemostasis was judged to be excellent/good in 509/702 (73%) bleeds. The numbers were revised to reflect the three additional bleeds as described above. These updates will be reflected in the label.

A total of 17 minor surgeries were performed in 10 subjects in Part A of the study. Eleven of these surgeries were dental extractions or other dental procedures. The remaining 6 surgeries included a repeat vasectomy, a colonoscopy, two procedures related to treatment of a cataract, incision and draining of an abscess, and a frenulum excision.

The pre-surgery dose of the study drug ranged from 1000 to 3000 IU. The maximum blood loss during surgery was 100 mL during the draining of an abscess. No subjects required blood transfusions. The adequacy of hemostasis during surgery was assessed as either "good" or "excellent" in all cases (for one surgery, the assessment was missing).

Reviewer Comment: This clinical reviewer agrees with the assessment of these minor surgeries. Note that the adequacy of hemostasis for major surgical procedures was evaluated in Part B of the study and is discussed in the next section.

Patient-reported outcomes data on quality-of-life, work and school productivity, and pain were collected for all patients.

Reviewer Comment: These PRO's were not validated and therefore will not be part of the labeling for this product.

Part B: Perioperative Management

Fourteen subjects underwent 17 major surgeries and 2 subjects only received JIVI for PK assessments but never underwent surgery.
One subject had an SAE was later re-screened as another Subject ID and underwent surgery.

There were 9 subjects with minor protocol deviations. Two subjects had major protocol deviations which included receiving the study pre-surgery and then dropping out of the study. All subjects were included in the safety population.

The majority of subjects were white and all were male. Only one subject was <18 years of age. Everyone were confirmed to have severe Hemophilia A and had received prior therapy for FVIII deficiency for at least 150 EDs prior to study entry.

Twelve of the major surgeries were orthopedic.

Table 11: Major Surgeries

Surgery Location	Blood Loss (mL) During/Post	Transfusion	Hemostatic Response During and Post
Left Shoulder Arthroscopy/Decompression	0/0	-	Good/Good
Left Hernia Repair	50/0	-	Excellent/ Excellent
Right Hip Arthroplasty	250-0	-	Excellent/ Excellent
Penile Prosthesis	50/0		Good/ Excellent
Removal Right Knee Prosthesis	590/930	Yes	Excellent/Good
Re-implantation of R Knee Prosthesis	1000/1430	-	Good/ Excellent
Left Knee Replacement	0/1100	Yes	Good/ Moderate
Right Knee Arthroplasty	400/2950	Yes	Good/Good
Right Ankle Arthroplasty	500/0	-	Good/Good
Right Knee replacement	0/70	-	Good/Good
Tooth Extraction	10/0		Excellent/ Excellent
Synovectomy	1000/1350	Yes	Good/-
Evacuation of Hematoma	600/255		Good/ Moderate
Synovectomy	30/0		Good/ Moderate
Right Knee Synovectomy	30/200		Excellent/ Excellent
Tooth Extractions	10/0		Excellent/ Excellent
Tooth Extractions	7/0		Excellent/ Excellent

Source: Adapted from BLA125661/0 CSR PH-37583 Table 9-1B page 153/1305

The initial doses administered ranged between 2000-5000 IU. The mean dose was 35 ± 9 IU/kg/infusion. The maximum total dose per kilogram per infusion was 51 IU/kg/infusion. 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. Four subjects received blood transfusions. These were in the orthopedic surgery procedures. There were six subjects who also received anti-fibrinolytics, 3 of them requiring transfusions.

Reviewer Comment: This clinical reviewer agrees with the assessment regarding adequacy of hemostasis for these major surgeries, which supports the proposed perioperative indication. There were four subjects who received blood transfusions post operatively due to the blood loss that occurred perioperatively. The blood loss observed is within the expected range for the major orthopedic surgeries. The dosing given for perioperative management is consistent with the recommendation of 40-50 IU/kg and

will be reflected in the label. Dosing calculations in the label was consistent with dosing calculations for perioperative and on-demand treatments in the study.

6.1.11.2 Analyses of Secondary Endpoints

Secondary endpoints are related to the safety of the product which will be reviewed in the Safety Analysis below.

6.1.11.3 Subpopulation Analyses

There were 22 subjects who previously received on-demand treatment prior to receiving routine prophylaxis in this study.

6.1.11.4 Dropouts and/or Discontinuations

Two subjects discontinued after a single dose of study drug. These two subjects were included in the safety population and excluded from the ITT population.

6.1.11.5 Exploratory and Post Hoc Analyses

N/A

6.1.12 Safety Analyses

6.1.12.1 Methods

There were 134 treated subjects in Part A that were included in the safety analysis population. Overall, there were 93 subjects (70.5%) achieving more than 50 exposure days (EDs). At least 50 subjects across all age groups were followed for at least 50 EDs. Subjects randomized to the every 7-day treatment regimen were expected to have 46 EDs.

In the 12-<18 years of age, 13 subjects were enrolled.

6.1.12.2 Overview of Adverse Events

Overall, 104 of the 134 subjects experienced at least one AE during Part A of the study. Twenty-one of the 134 subjects experienced at least one AE during the screening period prior to receiving the study drug.

There were 100 treatment emergent AEs (TEAEs). The highest overall incidence was seen in the MedDRA system organ class of “infections and infestations,” with the most common event being nasopharyngitis.

Partners of three subjects became pregnant during the study. There were no reported issues with the babies and no maternal complications were observed during pregnancy or delivery.

Twelve subjects experienced AEs considered to be drug related by the applicant. These included dry mouth, hypersensitivity, pruritis, “fuzzy thinking”, arthralgia, palpitations, overdose, increased transaminases, vessel site pruritus, abdominal pain, dyspnea.

Reviewer Comments: The AEs of hypersensitivity are likely related to the study drug. All other events are possibly related to the study drug as they were temporal.

6.1.12.3 Deaths

There were no deaths in this study.

6.1.12.4 Nonfatal Serious Adverse Events

Four subjects in the on-demand group experienced one SAE each. These included ethanol intoxication, pneumonia, ankle sprain, and acute pancreatitis.
In the prophylaxis group, 10 subjects experienced 11 SAEs. These included drug hypersensitivity, tendon rupture, bile duct stone, hemarthrosis, chest pain, gastroenteritis, injury, arthropathy, and overdose.

Two subjects had hypersensitivity reactions. No subject had anaphylaxis. One event was observed after the first exposure and the other event occurred after the 4th exposure. These two subjects discontinued the study drug. One of the subjects had anti-drug antibodies.

Reviewer Comments: The AEs of hypersensitivity are likely related to the study drug. All other events are possibly related to the study drug as they were temporal.

6.1.12.5 Adverse Events of Special Interest (AESI)

No subject was reported to have developed a FVIII inhibitor during Part A of the study. Antibodies to the study drug were measured. All results were negative. One subject reported an allergic reaction and had transient anti-drug antibodies. Transient positive antibody responses against the study drug were detected in 5 other subjects.

One subject had an inhibitor detected at screening. This event was reported as an SAE and the subject never received the study drug. Two subjects (1.5%) had hypersensitivity reactions. One subject reported an allergic reaction which occurred after the 4th dose of the study drug and experienced headache, abdominal pain, dyspnea, and flushing which resolved the same day. Anti-drug antibodies and anti-PEG antibodies were positive and FVIII inhibitor antibodies were negative. This subject discontinued the study. The second subject experienced flushing, exanthema, and paresthesias after his first dose. This resolved within ten minutes. No medication was used to treat the reaction. The subject withdrew and dropped out of the study.

FVIII inhibitor antibodies were negative. Transient positive PEG antibody responses were detected in six subjects. Six subjects had transient anti-drug antibodies. Of those that were measured, two had subjects had anti-drug neutralizing antibodies above >0.6.

6.1.12.6 Clinical Test Results

Safety lab evaluations were performed at screening, Visit 4, 8 and 36. There were 18 clinical chemistry labs that had abnormally low values. There were 63 hematologic values that were abnormally low. There were 109 clinical chemistry values that had abnormally high values. The majority was the glucose value. There were 40 hematologic values that were abnormally high values. None of these were clinically relevant in the subject population. None of these were reported as AEs by the investigator.

Reviewer Comment: These abnormal lab values were judged not to be clinically relevant by this clinical reviewer. Most were transient and resolved by the end of study visit. The high glucose values could be related to a non-fasting state when the specimen was drawn.

6.1.12.7 Dropouts and/or Discontinuations

As stated above, there were two SAEs where one experienced a hypersensitivity reaction after the fourth dose of the study drug and one subject after the first dose. Both subjects discontinued the study after the reaction. One of these subjects had positive Anti-PEG antibodies and Anti-drug antibodies.

Another subject developed a rash and the study drug was withheld due to this AE.

Part B:
The safety population for Part B included 14 subjects who underwent surgery and 2 subjects who received the study drug for PK assessment but never underwent surgery. Treatment emergent AEs were reported in 12 of the 16 subjects. Three subjects experienced four SAEs. These included non-cardiac chest pain, anti-FVIII antibodies, and a hematoma. The highest overall incidence of 31.3% was seen in AEs referring to the MedDRA SOC “injury, poisoning and procedural complications” with the most common events being procedural hemorrhage and procedural pain.

Three subjects experienced four SAEs judged by the applicant as drug-related during Part B. One subject experienced a subcutaneous hemorrhage/hematoma. The dose of the study drug was increased and resolved. One subjects had a positive FVIII antibody. Another subject had flushing during the PK assessment and a positive FVIII antibody. One subject had non-cardiac chest pain which resolved.

Reviewer Comment: The subject with the hematoma had an inhibitor titer of 0.5 BU during screening. The subject had surgery for soft tissue release and had another surgery to evacuate the hematoma that developed after the first surgery. Another FVIII product was given after hematoma evacuation for better hemostatic control. The inhibitor titers that were drawn prior to the new FVIII product showed a titer of 0.7 BU. Post surgically, this subject had received 29 infusions of the study drug. Seven weeks after switching, a FVII inhibitor antibody titer was positive for a low titer inhibitor of 2.7 BU. This clinical reviewer judges this to be possibly related to the study drug, but likely due to the factor product that the subject was switched to after his procedure.

The subject with flushing was reported to have this event at the PK assessment. This subject had a low titer inhibitor of 1.7 BU. This sample was collected before surgery after one dose of the study drug. Another FVIII product was given in the post-operative period. This high titer resolved within two weeks. This is judged to be likely due to the study drug.

The subject with non-cardiac chest pain had received a PK assessment and had this AE 23 days after the infusion. This clinical reviewer judges this to be non-related to the study drug.

There were no deaths in Part B of the study.

6.1.13 Study Summary and Conclusions

Prophylactic infusion with JIVI was effective for prevention of bleeds at dose intervals of 2x/week and every 5 days, as compared with a non-randomized control group of patients receiving on-demand treatment. Subjects in the 2x/week forced and every 5 day treatment groups experienced comparable bleeding control. Subjects in the 2x/week

failed group had a high ABR despite being switched from a median dose of 25.6 IU/kg regimen to 38.9 IU/kg. Under standard of care, these subjects would have individualized prophylaxis through escalation of doses or frequency to reduce the frequency of bleeding. Subjects in the every 7-day treatment group had bleeding events which caused 25% of those in that group to discontinue treatment as they had a higher mean ABR. Given the high ABR rate in the every 7-day group, this dosing regimen will not be recommended and will not be included in label. A starting dose of 30-40 IU/kg twice weekly is recommended, and based on the bleeding profile, the patients' regimen may be modified to 45-60 IU/kg every 5 days.

Most bleeds were treated with 1-2 infusions and hemostasis was judged to be excellent or good.

The study drug provided 'good' or 'excellent' hemostatic control during 17 major surgeries in adults and adolescents with severe hemophilia A. The blood loss was within expected ranges.

Dose calculations for perioperative and on-demand dosing were based on target dose and weight and the recommendations for dose calculations will be based on these dose calculations.

No subject developed inhibitory antibodies to FVIII during the study. No unexpected adverse events occurred. There were two drug-related serious adverse reactions, notably hypersensitivity reactions, which is an expected risk. These risks will be discussed in the label in the Warnings and Precautions section. Overall, JIVI exhibited a favorable safety and tolerability profile.

6.2 Trial #2 (Protocol 38453/Study13024)

A multicenter, partially randomized, open label trial investigating safety and efficacy of on-demand and prophylactic treatment with JIVI in Severe Hemophilia A- EXTENSION STUDY (ongoing)

6.2.1 Objectives (Primary, Secondary, etc)

Optional Part A: To assess the long term safety of BAY 94-9027 over at least 100 accumulated exposure days (ED) (main study plus extension)

Part B extension: To assess the safety and efficacy of JIVI in the prevention of bleeding during major surgical procedures

6.2.2 Design Overview

This study was a multicenter, open-label, uncontrolled study to evaluate the PK, safety, and efficacy of treatment with the study for prophylaxis and treatment of bleeds and surgeries in previously treated adults and adolescents with severe Hemophilia A.

Part A Extension: Prophylaxis subjects were either to continue their prophylaxis or had the option of switching to the one of the other prophylaxis regimens. Subjects receiving prophylaxis in the Part A extension were to receive JIVI every 7 days, every 5 days, or twice weekly using a dosage in the range specified for that dosing frequency during the Part A main trial (60 IU/kg for every 7 days; 45-60 IU/kg for every 5 days; 30-40 IU/kg for

2x/week). On demand subjects could continue on-demand treatment or had the option of a one-time switch to one of the prophylaxis regimens.

Part B Extension: Subjects requiring major surgery may have chosen to participate in the Part B extension.

6.2.3 Population

Key inclusion criteria were as follows:
1. Male; 12 to 65 years of age
2. Subjects with severe hemophilia A
3. Previously treated with FVIII concentrate(s) (plasma derived or recombinant) for a minimum of 150 ED

Key exclusion criteria were as follows:
1. Current evidence of inhibitor to FVIII with a titer ≥ 0.6 BU/mL, measured by the (b) (4) Bethesda assay at the time of screening (central laboratory)
2. History of inhibitor to FVIII with a titer ≥ 0.6 BU, or clinical history suggestive of inhibitor requiring modification of treatment. Subjects with a maximum historical titer of 1.0 BU on a single measurement but with at least 3 subsequent successive negative results (< 0.6 BU) thereafter were eligible.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Same as with Trial 1.

6.2.5 Directions for Use

Subjects receiving prophylaxis in the Part A extension were to receive either every 7 days, every 5 days, or 2x/week regimen using a dosage in the range specified for that dosing frequency during the Part A main trial (60 IU/kg for every 7 days; 45-60 IU/kg for every 5 days; 30-40 IU/kg for 2x/week).

For surgeries, the dose was 50 IU/kg given <60 min before the start of the procedure; 15-50 IU/kg repeated as needed.

6.2.6 Sites and Centers

The Part A extension of the main trial was conducted at 52 study centers in 18 countries. Each center enrolled at least 1 subject who was treated in the extension. The subjects who received treatment during the extension were from the following participating countries (number of subjects in parentheses): Austria (5), Belgium (2), Colombia (4), Germany (3), Denmark (5), France (5), United Kingdom (7), Israel (15), Italy (5), Japan (11), South Korea (7), Netherlands (6), Norway (3), Poland (3), Singapore (9), Turkey (4), Taiwan (3), and the United States (24).

The subjects participating in Part B (main trial and extension) were from the following countries: Austria (1), France (1), United Kingdom (1), Israel (3), Italy (3), Netherlands (1), Romania (2), Turkey (1), Taiwan (1), and the United States (5).

6.2.7 Surveillance/Monitoring

As above in the Main Study.

6.2.8 Endpoints and Criteria for Study Success

There were no pre-determined efficacy objectives for the Part A extension. No formal efficacy analysis was performed as subjects had different treatment regimens and visit frequency.

For Part B extension, efficacy endpoints included blood loss, transfusion requirements, change in hemoglobin, investigator response to treatment (excellent, good, moderate, or poor), and study drug usage.

6.2.9 Statistical Considerations & Statistical Analysis Plan

As above in Section 6.2.8. All efficacy data were to be summarized with descriptive statistics.

6.2.10 Study Population and Disposition

A total of 126 subjects (on-demand [N=18]; prophylaxis [N=108]) completed treatment during the main trial, Parts A and B. A total of 121 subjects received treatment during the extension period of the main trial. These subjects were also eligible for participation in the Part B extension if they required major surgery and were willing to use the study drug for hemostasis during surgery.

A total of 78 subjects had minor protocol deviations. There were no major protocol deviations during the extension.

6.2.10.1 Populations Enrolled/Analyzed

Part A Extension: A total of 121 subjects entered the Part A extension.

6.2.10.1.1 Demographics

Refer to the main trial for complete demographics.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Severe Hemophilia A was confirmed for all subjects at screening.

6.2.10.1.3 Subject Disposition

There were 14 subjects in the on-demand group. There were 24 subjects in the 2x/week dosing; four did not complete the extension due to two AEs, one withdrawal, and one that was lost to follow up. Thirty-seven subjects were in the every 5-day prophylaxis group, and one did not complete the extension due to subject withdrawal. Twenty-nine subjects were in the every 7-day prophylaxis group; one did not complete the extension due to discontinuation by the applicant for non-adherence to the study protocol. There were 17 subjects who were on variable frequency prophylaxis. The variable frequency group included those subjects who received more than one regimen during the extension phase after a week of being enrolled (for example, a subject could have received twice weekly regimen in the second week in the extension phase and switched to the 5-day regimen at any time point).Thirty seven subjects completed the extension and 78 subjects were ongoing participants.

Three subjects who had received on-demand treatment during the Part A main trial switched to 2x/week dosing in the extension at doses appropriate for their weight. One subject switched from every 7 days and one from 2x/week to every 5 days dosing, and 5 subjects switched from other groups to the every 7 days group. These subjects were not considered variable frequency subjects by switching within 1 week from start of extension.

Most prophylaxis subjects did not change their dose during the Part A extension.

There were 3 additional major surgeries that occurred during the extension.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

Fourteen subjects received on-demand treatment during the Part A extension and all were included in the ITT population. Subjects in the on-demand treatment arm had 514 total bleeds over the reporting period for this interim analysis which comprised descriptive statistics. The median was 40.0 total bleeds (range:10-63), corresponding to an annualized bleeding rate (ABR) of 32.96. The mean ABR was 32.41.There were no subjects in the on-demand group that had zero bleeds.

One hundred seven subjects began treatment in the Part A extension in one of the prophylaxis treatment arms and all were included in the ITT population. Subjects in the prophylaxis treatment arms had 428 total bleeds over the reporting period for this interim analysis. The median was 1.0 total bleeds (range: 0-45), corresponding to a median ABR of 1.17; the mean ABR was 3.76.

For analyses purposes, subjects were defined based on the dosing regimen: twice a week, 5 days, 7 days and variable frequency. The variable frequency group included those subjects who received more than one regimen during the extension phase a week after they were enrolled into the extension phase (for example, a subject could have received twice weekly regimen in the second week in the extension phase and switched to the 5 day regimen at any time point).

The 428 total bleeds correspond to a median and mean ABRs, respectively, of 2.21/3.95 for the 2x/week group, 1.17/4.41 for the every 5 days group, 0.54/1.56 for the every 7 days group, and 3.94/5.83 for the variable frequency group.

Table 12: ABR rates for subjects on Extension study

	Variable frequency	2x/week	Every 5 days	Every 7 days
N (number of subjects)	17	24	37	29
# of total bleeds	105	93	192	38
Mean ± SD	5.83 ± 7.05	3.95±4.83	4.41±6.79	1.56±3.72
Median (range)	3.94 (0-28)	2.21 (0-16.2)	1.17 (0-34.9)	3.85 (0-53.1)

Source: Adapted from BLA125661/0 CSR PH-37453 Table 9-1B page 57/109

Reviewer Comment: *The variable frequency group were subjects who changed the treatment regimen at least once. This group is difficult to analyze since their dosing changed and is likely to be individualized. The ABRs were comparable to the results in*

the Main study, with the exception of the 7-day regimen. The mean ABR rates are much lower (1.56) in the 7-day regimen group in the extension study; however, of the 43 subjects in the main study only 29 continued in the extension study with a 7-day regimen. The reviewer concludes that the "improved" ABR in the 7-day regimen may be the result of selection or switching of subjects who had an unfavorable bleeding profile in the main study to more frequent regimens or as a result of drop out. The reviewer concludes that patients could be individualized to a 7-day regimen if their bleeding profile permits individualization to this less frequent regimen. From this study design, it would be difficult to identify subjects who are likely to do well on this 7-day regimen and thus will not be included in the label.

Since this study is ongoing and comparable to the main study results, the extension study will be omitted from the label, as it does not add anything further to the efficacy results.

The three major surgeries in the extension trial were orthopedic surgeries. The assessment of hemostasis was good for all three surgeries with minimal blood loss. None of the subjects received blood transfusions.

6.2.11.2 Analyses of Secondary Endpoints

N/A

6.2.11.3 Subpopulation Analyses

N/A

6.2.11.4 Dropouts and/or Discontinuations

Six subjects discontinued the extension study. Two subjects withdrew. One subject was lost to follow up. One was a sponsor decision due to challenges with subject adherence to the protocol. There were two subjects that discontinued due to an AE. The first subject had an elevated ALT. The second subject had migratory back pain which required prolonged hospitalization.

One subject in Part B extension withdrew due to an AE of worsening hematoma.

Reviewer comment: In the reviewer's opinion, none of these subjects discontinued the study treatment for AEs that were related to the product.

6.2.11.5 Exploratory and Post Hoc Analyses

N/A

6.2.12 Safety Analyses

6.2.12.1 Methods

There were 121 subjects evaluated in the Extension phase. Subjects participated in the extension study for variable periods of time.

6.2.12.2 Overview of Adverse Events

There were 108 subjects that experienced an AE. Twenty of the 121 subjects experienced 23 SAEs. Similar to the Main study, the highest overall incidence of AEs was in "infections and infestations" (53.7% of all subjects) with the most common event

being nasopharyngitis(27.3% of all subjects). Almost all (72.8%) subjects with treatment-emergent AEs experienced AEs with a maximum intensity that was either mild or moderate.

Five subjects experienced 7 AEs that were judged by the investigator to be study-drug related. These included an elevated ALT (2 subjects), pruritus, thrombocytopenia, back pain, arthralgia, and erythema multiforme.

Reviewer Comment: *This clinical reviewer judged these AEs as follows: The two subjects with elevated ALTs also had Hepatitis C and on other medication which was the likely cause for the elevated ALT. The subject with pruritus was likely caused by the study drug as this SAE occurred at the injection site. The arthralgia was not likely due to the study drug. The erythema multiforme occurred after approximately 500 days of treatment on study and not likely due to the study drug.*

During Part B, the highest overall incidence AE related to injury, poisoning, and procedural complications with the most common event being procedural pain.

6.2.12.3 Deaths

There were no deaths.

6.2.12.4 Nonfatal Serious Adverse Events

There were 20 subjects who experienced 23 total SAEs. All of the SAEs were reported to have been resolved or recovering by the end of the observation period.

Reviewer Comment: All of the SAEs were judged by this clinical reviewer as not related to the study drug.

There were no new SAEs reported for the Part B extension safety population.

6.2.12.5 Adverse Events of Special Interest (AESI)

There were no AEs of special interest during the extension study. No subject developed FVIII inhibitors during the extension study.

No subjects had positive anti-drug antibodies or anti-PEG antibodies.

6.2.12.6 Clinical Test Results

All of the laboratory value shifts were not considered clinically significant, apart from the elevated ALTs that were reported as AEs.

6.2.12.7 Dropouts and/or Discontinuations

As above.

6.2.13 Study Summary and Conclusions

Prophylactic infusion with JIVI was effective for the treatment of bleeding events and treated with 1-2 infusions. The overall mean ABR for Part A extension was 32.4 for the on-demand group and 3.76 for the prophylaxis group. The overall median ABR for Part A extension was 32.96 for the on-demand group and 1.17 for the prophylaxis group. Treatment with JIVI provided adequate hemostatic control during three major surgeries.

No subject developed inhibitory antibodies to FVIII during the extension. No subjects had anti-drug or anti-PEG antibodies. Since the main study is the primary study and the extension results were comparable, this analysis will not be included in the label.

6.3 Trial #3 (Protocol 38440/Study15912)

A multi-center, phase III, uncontrolled, open-label trial to evaluate the pharmacokinetics, safety, and efficacy of JIVI for prophylaxis and treatment of bleeding in previously treated children (age <12 years) with severe hemophilia A.

6.3.1 Objectives (Primary, Secondary, etc)

The main objective of the study was to evaluate PK, safety, and efficacy of JIVI for prophylaxis and treatment of bleeding in previously treated patients with hemophilia A.

6.3.2 Design Overview

This was a multicenter, open-label, uncontrolled study to assess the PK, efficacy, and safety of treatment with JIVI for prophylaxis and treatment of bleeding in children with severe hemophilia. At least 50 pediatric subjects in 2 age subgroups who had been previously treated for >50 EDs with any FVIII concentrate were enrolled.

Subgroup 1 (n=25): age 6 to <12 years; Subgroup 2 (n=25): age <6 years.

The total study duration (excluding an up to 6-week screening period) was dependent on the amount of time required for the subject to accumulate a minimum of 50 EDs, and was expected to be at least 6 months. All subjects were offered participation in an open-label extension study to allow observations for at least an additional 50 EDs.
All subjects were to receive prophylactic administration of JIVI at least one day each week. The starting dosing regimen for each individual subject was selected by the investigator, so that treatment began with prophylaxis administered either 2x/week (25 IU/kg), every 5 days (45 IU/kg), or every 7 days (60 IU/kg). Once a dosing regimen was chosen, the doses and dose frequency were allowed to be adjusted at any time and at the discretion of the treating physician to meet the subject's clinical needs to maintain adequate bleed control. PK assessments occurred in 12 subjects from each age group.

6.3.3 Population

The trial enrolled previously treated children (≤12 years) with hemophilia A and a FVII activity level of <1 %. The subjects were stratified into two age groups: 0- <6 years and 6-12 years.

The inclusion criteria are noted below:
1. Male, age <12 years to be enrolled in 2 subgroups:
   - age 6 to <12 years
   - age <6 years
2. Severe hemophilia A defined as <1% Factor VIII concentration
3. >50 ED with any FVIII concentrate(s)
4. Willingness and ability of subjects and/or parents to complete training in the use of the EPD and to document infusions during the study
5. Written informed consent by parent/legal representative. Assent was to be sought from subjects, if appropriate

Key exclusion criteria are noted below:
1.Current evidence of inhibitor to FVIII at the time of screening. Subjects should not have received FVIII within 72 hours prior to the collection of screening samples and should have had FVIII administered within the prior 2-3 weeks.
2. History or presence of FVIII inhibitors. Inhibitor to FVIII was defined as a titer >0.6 BU/mL or clinical history suggestive of inhibitor requiring modification of treatment. (Subjects with a maximum historical titer of <1.0 BU on no more than 1 occasion with the classical Bethesda assay but at least 3 subsequent negative results [<0.6 BU] were eligible.)

6.3.4 Study Treatments or Agents Mandated by the Protocol

The following investigational medicinal product was used in the trial: JIVI
The investigational product was supplied as a lyophilized powder in glass vials. Study vials contained 250 IU, 500 IU, or 1000 IU of FVIII activity.

6.3.5 Directions for Use

The prophylaxis regimens administered were: 2x/week (25 IU/kg), every 5 days (45 IU/kg), or every 7 days (60 IU/kg).

The dose regimen to be used for treatment of breakthrough bleeds depended on the severity of the bleed, the location, the subject's prior experience with treatment of bleeding events, and the treating physician's recommendations. If a bleed occurred on a day of the planned injection, the subject was to treat the bleed instead of receiving the scheduled prophylactic infusion. If in the assessment of the subject/parent and investigator the dose of 60 IU/kg did not provide sufficient protection against bleeds, the dose was not to be increased. Subjects had the option of changing their infusion schedule to either the every 5 days or 2x/week schedules and using a dosage in the range specified for that dosing frequency. Subjects in the every 5 days treatment group also had the option to change to a 2x/week infusion regimen. The dose could be increased up to 60 IU/kg for those receiving prophylaxis every 5 days and 2x/week.

Any subject receiving treatment on the every 5-day or every 7-day infusion schedule who experienced 2 breakthrough (spontaneous, no identified trauma) joint and/or muscle bleeds within any 3-month period on that regimen, during any part of the study, was to increase the dose or increase the dosing frequency.

The study drug was also used for any minor surgery that was required during the course of the study.

6.3.6 Sites and Centers

The study was conducted at 31 study centers in 13 countries. The subjects were from the following participating countries: Argentina (1), Austria (1), Belgium (2), Bulgaria (3), Canada (2), United Kingdom (4), Israel (1), Italy (3), Lithuania (1), Netherlands (2), Poland (2), Romania (3), and the United States (6).

6.3.7 Surveillance/Monitoring

The sponsor/designee monitored the site activity to verify that the:
- Data were authentic, accurate and complete
- Safety and rights of subjects were being protected

- Study was conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements were met.

Before enrollment in the trial and prior to conduct of any trial-related procedures/activities, the parent(s) of the patient had to sign the informed consent document after having received written and verbal information about the trial, in accordance with GCP and local requirements.

A patient was withdrawn if the following applied:
-At their own request or at the request of their parent/legal representative
-At any time during the study and without giving reasons, a subject may have declined to participate further. The subject was not to suffer any disadvantage as a result.
-If, in the investigator's opinion, continuation of the study would have been harmful to the subject's well-being
- A positive inhibitor result at the Screening (Visit 1) or Baseline (Visit 2) visits
- At the request of the sponsor
- If, in the judgment of the investigator or the sponsor, the subject was not compliant with the protocol
- Development of an inhibitory antibody to FVIII or the study drug that neutralized activity sufficiently to interfere with effective treatment or required use of a bypassing agent to treat bleeds
- Lack of response to treatment (other than from an inhibitor)
- Severe hypersensitivity reaction
- Failure to comply with scheduled appointments for study-related testing or with EPD data entry to an extent that compromised collection of critical data

6.3.8 Endpoints and Criteria for Study Success

The primary endpoint was the ABR.
Secondary endpoints included assessment of response to treatment of a bleed, frequency of inhibitor development, PK and recovery, and impact on quality of life.

6.3.9 Statistical Considerations & Statistical Analysis Plan

Evaluation of all endpoints was based on descriptive analyses.

6.3.10 Study Population and Disposition

The trial population consisted of males with Hemophilia A.

6.3.10.1 Populations Enrolled/Analyzed

A total of 65 subjects were screened for enrollment in the main study. Three subjects initially failed screening but were successfully re-screened and enrolled in the main study resulting in 68 subject patient identification (PID) numbers. Five subjects were not eligible, and 2 subjects had logistical difficulties, resulting in 61 PTPs (32 in the age group 0 to <6 years and 29 in the age group 6 to <12 years) that actually participated in the main study.

Across both age groups, 53 of these subjects completed at least 50 EDs with the study drug during the main study (including 25 subjects <6 years of age and 28 subjects between the ages of 6 and <12).

6.3.10.1.1 Demographics
Thirty-two subjects were in the 0-<6 years age group with a median age of three years and 29 subjects were in the 6-12 years age group with a median age of nine years. The majority of subjects were White (n=55).

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All subjects were males with severe Hemophilia A. All subjects were previously treated patients with 50 EDs to other FVIII products. Eleven of 61 subjects had a target joint present at the time of enrollment.

6.3.10.1.3 Subject Disposition

In the main study, 61 subjects received at least one dose of treatment with study drug and were included in the Safety population. One subject discontinued after a single dose of study drug and was excluded from the ITT population because no efficacy data for this subject were available for evaluation.
At the start of the study, 18 subjects began treatment on the 2x/week regimen, 27 subjects on the every 5-day regimen, and 15 subjects on the every 7-day regimen.

Fifty-one of 60 subjects (85%) in the ITT population remained at their initial dose frequency at the end of the study. Eight subjects, all in the every 7 day treatment group, increased their dose frequency. These subjects increased their dose frequency to either every 5 days (6 subjects) or to 2x/week treatment (2 subjects). One of the 27 subjects from the every 5 days group decreased frequency to every 7 days.

At the end of the main study, 20 subjects were in the 2x/week regimen, 32 in the every 5 days regimen, and 8 in the every 7 days regimen.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)
The primary endpoint was to assess the annualized bleed rate.

Table 13: Mean and Median ABR for Pediatric Age groups

	0-<6 years	6-12 years	Total
Number of subjects	32	28	60
Number of subjects with bleeds	25	20	45
Number of bleeds	72	68	140
Mean ABR (SD)	8.55 (15.73)	3.77 (3.63)	6.32 (11.91)
Median ABR [Min; Max]	2.68 [0,74.6]	2.92 [0, 11]	2.87 [0, 74.6]

Source: Adapted from BLA125661/0 CSR PH-38440 Table 9-1 page 69/505

Of the 61 subjects successfully screened for the study, 32 subjects in the <6 years old group and 28 8subjects in the 6 to <12 years old group received treatment during the main study. These 60 subjects had a total of 140 bleeds, of which 88 (63%) were

traumatic bleeds and 52 (37%) were spontaneous bleeds. The median ABR was similar between the two age groups. Fifteen subjects had no bleeding (across all dosage regimens).

Table 14 : Mean and Median ABR for Pediatric Age groups

Dosing Regimen	Twice weekly	Every 5 days	Every 7 days
<6years			
Mean (SD) ABR	6.84 (12.99)	14.10 (22.74)	2.53 (2.56)
Median ABR	1.78	3.85	1.37
6-12 years			
Mean (SD) ABR	2.89(3.69)	3.67(3.02)	2.19
Median ABR	0.99	3.03	2.19

Reviewer Comment: The sample size for each of the groups is small, but subjects over 6 years of age on the twice weekly regimen had an acceptable ABR. There was only one subject in the every 7 day regimen, therefore, no assessment can be based off of this one subject.

The nine subjects who had a variable frequency of dosing due to bleeding (40 of the 140 bleeds) had a higher ABR.

There was a total of 52 spontaneous bleeds. The median ABR for spontaneous bleeds was zero. There were 88 traumatic bleeds and the median ABR was 1.35. There were 56 joint bleeds and the median ABR was zero. Forty percent of the bleeds were located in the joint. In the 6 to <12 years old group, 50% of bleeds were reported as joint bleeds, whereas in the <6 years group most bleeds were skin or mucosa bleeds (41.7%). Ten percent of all bleeds were of severe intensity. A total of 118 bleeds were treated with 1 infusion (84.3%), 11 bleeds (7.9%) were treated with 2 infusions, and 11 (7.9%) required 3 or more infusions.

Reviewer Comment: It is expected that the majority of bleeds were joint bleeds in the older age group.

6.3.11.2 Analyses of Secondary Endpoints

N/A

6.3.11.3 Subpopulation Analyses

N/A

6.3.11.4 Dropouts and/or Discontinuations

There were seven subjects that experienced an AE which led to discontinuation. Six of the seven had a SAE. Three subjects who discontinued experienced a hypersensitivity reaction. Three subjects experienced bleeding not responsive to the study drug. Two subjects also experienced bleeding not responsive to study drug but were not reported as an SAEs. One subject discontinued due to the parent's decision.

6.3.11.5 Exploratory and Post Hoc Analyses

N/A

6.3.12 Safety Analyses

6.3.12.1 Methods

All 61 subjects that were treated in the main study were included in the Safety population.

6.3.12.2 Overview of Adverse Events

A total of 50 out of 61 (82%) subjects reported an AE. Most of the adverse events (86%) were judged by the investigator to be of mild and moderate severity. Nine subjects had AEs that were judged by the investigator to be likely related to the study drug. Seven subjects had adverse events that led to withdrawal of the subject.

Across both age groups, the highest overall incidence of AEs was seen in AEs of "infections and infestations" (47.5% of all subjects) with the most common event being upper respiratory tract infection (11.5% of all subjects).

Reviewer Comment: This reviewer judges that these AEs are not likely related to the study drug.

6.3.12.3 Deaths

There were no deaths reported.

6.3.12.4 Nonfatal Serious Adverse Events

Over the course of the main study, 11 of the 61 subjects (18.0%) experienced 22 SAEs. Eight subjects in the <6 years old group experienced a total of 14 SAEs; in 5 of the subjects, the SAEs were considered to be related to the study drug by the investigator and led to study discontinuation. These SAEs included hypersensitivity reactions, persistent hematomas, anti-PEG antibodies, and infection of port-a-catheter. Three subjects in the older age group experienced a total of 8 SAEs. One of these events led to discontinuation. These SAEs included an allergic reaction, intracranial bleed, and gastroenteritis. All SAEs resolved by the end of the main study.

6.3.12.5 Adverse Events of Special Interest (AESI)

No subject developed a FVIII inhibitor during the main study. There were eight subjects who developed loss of efficacy of the study drug. Three subjects had hypersensitivity reactions or antibody formation which then resulted in loss of efficacy, whereas two subjects had increased bleeding/bruising/poor recovery and suspected to have loss of efficacy.

An expansion group or Part 2 of the pediatric study included 12 additional PTPs below 6 years of age. This part of the study was introduced to further evaluate the safety of the study drug with a focus on potential immunogenicity of the study drug in this age group. Part 2 subjects were treated with study medication for 12 weeks. In this group, one subject developed hypersensitivity with positive baseline anti PEG IgM antibodies.

The table below shows the eight subjects with loss of efficacy and the 4 subjects with hypersensitivity. Ten out of the 12 subjects had an antibody present. Six subjects had anti-PEG IgM antibodies and/or positive neutralizing antibodies at baseline. In one subject, no anti-drug antibody was detected.

All of the subjects with loss of efficacy were under 6 years of age. Three of the four subjects with hypersensitivity were under 6 years of age.

Table 15: Pediatric Subjects with Loss of Efficacy and Hypersensitivity				
Subject number Regimen / Starting Dose	**AE (EDs before onset of AE) Action taken (EDs)**	**Antibody type**	**Pre-treatment positive ADA: titer**	**Titer (EDs before measurement)**
Subject (b) (6) (3-year-old, White) Every 5 days / 55 IU/kg	spontaneous hematoma (ED 3) drug specific Ab present (ED 4) withdrawal (ED 4)	Anti-BAY 94-9027:	negative	**8** (3 EDs)
		Anti-BAY 94-9027 NAb:	**not tested**	**2.2 BU** (3 EDs)
		Anti-PEG:	negative	**8** (3 EDs)
		Anti-PEG IgM:	negative	**16** (3 EDs)
Subject (b) (6) (3-year-old, White) Every 5 days / 55 IU/kg	hemarthrosis (ED 3) drug specific Ab present (ED not available) withdrawal (ED 3)	Anti-BAY 94-9027:	negative	negative
		Anti-BAY 94-9027 NAb:	negative	An inconclusive unconfirmed positive result for BAY 94-9027 NAb in the final sample. NAb: > **2 BU**
		Anti-PEG:	negative	negative
		Anti-PEG IgM:	negative	negative
Subject (b) (6) (3-year-old, White) 2x/week/ 35 IU/kg	drug specific Ab present (ED 2) withdrawal (ED 8)	Anti-BAY 94-9027:	negative	**16** (8 EDs)
		Anti-BAY 94-9027 NAb:	negative	**4.6 BU** (8 EDs)
		Anti-PEG:	negative	**16** (8 EDs)
		Anti-PEG IgM:	negative	**128** (5 EDs); **128** (6 EDs); **32** (8 EDs)
Subject (b) (6) (3-year-old, White) 2x/week/25 IU/kg	contusion (ED 3) withdrawal (ED 4)	Anti-BAY 94-9027:	negative	negative
		Anti-BAY 94-9027 NAb:	negative	negative
		Anti-PEG:	negative	negative
		Anti-PEG IgM:	negative	negative
Subject (b) (6) (4-year-old, White) Every 5 days/ 45 IU/kg	N/A Parents withdrawal due to perceived LoE (ED 6)	Anti-BAY 94-9027:	negative	negative
		Anti-BAY 94-9027 NAb:	negative	negative
		Anti-PEG:	negative	negative
		Anti-PEG IgM:	**4**	negative
Subject (b) (6) (2-year-old, White) 2x/week/ 40 IU/kg	drug ineffective (ED 2) withdrawal (ED 6)	Anti-BAY 94-9027:	negative	**16** (2 EDs); **16** (4 EDs); **16** (5 EDs); **4** (6 EDs)
		Anti-BAY 94-9027 NAb:	negative	**3 BU** (2 EDs); **9.8 BU** (3 EDs); **3.9 BU** (4 EDs); **3.6 BU** (5 EDs); **2 BU** (6 EDs)
		Anti-PEG:	negative	**16** (2 EDs); **64** (ED 3); **16** (4 EDs); **16** (5 EDs); **4** (6 EDs)
		Anti-PEG IgM:	**8**	**64** (2 EDs); **128** (3 EDs); **64** (4 EDs); **32** (5 EDs); **64** and **2** (6 EDs)
Subject (b) (6) (5-year-old, White) 2x/ week/ 45 IU/kg	drug ineffective (ED 5) withdrawal (ED 5)	Anti-BAY 94-9027:	negative	**32** (2 EDs); **64 and 4** (5 EDs)
		Anti-BAY 94-9027 NAb:	negative	**8.6 BU** (2 EDs); **13 and 1.8 BU** (5 EDs)

Table 15: Pediatric Subjects with Loss of Efficacy and Hypersensitivity				
Subject number Regimen / Starting Dose	**AE (EDs before onset of AE) Action taken (EDs)**	**Antibody type**	**Pre-treatment positive ADA: titer**	**Titer (EDs before measurement)**
		Anti-PEG:	negative	**32** (2 EDs); **64** and **4** (5 EDs)
		Anti-PEG IgM:	negative	**128** (2 EDs); **128** and **4** (5 EDs)
Subject (b) (6) (5-year-old, Asian) 2x/week/ 60 IU/kg	drug ineffective (ED 1) withdrawal (ED 3)	Anti-BAY 94-9027:	negative	negative
		Anti-BAY 94-9027 NAb:	(un-confirmed)	(unconfirmed)
		Anti-PEG:	negative	negative
		Anti-PEG IgM:	**1**	negative
Subject (b) (6) (5-year-old, White) 2x/week/ 25 IU/kg	hypersensitivity (EDs 2/3) [b], anti-FVIII ab positive (EDs 2/3) [b]; withdrawal (ED 5)	Anti-BAY 94-9027:	negative	**16** (ED 5,17 days after EOT, neg 2 months after EOT)
		Anti-BAY 94-9027 NAb:	negative	**12.1 BU** (ED 5, 2 days after EOT), **2.8 BU** (ED 5, 17 days after EOT)
		Anti-PEG:	negative	**16** (ED 5, 17 days after EOT, neg 2 months after EOT)
		Anti-PEG IgM:	**4**	**256 and 32** (ED 5)
Subject (b) (6) (2-year-old, White) Every 5 days/ 45 IU/kg	hypersensitivity (ED 3/4) [c], withdrawal (ED 4)	Anti-BAY 94-9027:	negative	negative
		Anti-BAY 94-9027 NAb:	negative	**3 BU** (4 EDs, 6 months after EOT),
		Anti-PEG:	negative	**4** (4 EDs, 6 months after EOT)
		Anti-PEG IgM:	**16**	**4** (4 EDs**,** 6 months after EOT)
Subject (b) (6) (4-year-old, White) 2x/week/ 30 IU/kg	hypersensitivity (ED 3), withdrawal (ED 3)	Anti-BAY 94-9027:	negative	**32** (2 EDs); **32** (3 EDs)
		Anti-BAY 94-9027 NAb:	negative	**2 BU** (2 EDs); **3.4 BU** (3 EDs)
		Anti-PEG:	negative	**32** (2 EDs); **32** (3 EDs)
		Anti-PEG IgM:	**2**	**64** (2 EDs); **128** (3 EDs)
Subject (b) (6) (6-year-old, White) Every 7 days/ 60 IU/kg	Hypersensitivity (1) drug withdrawn (1)	Anti-BAY 94-9027:	negative	negative
		Anti-BAY 94-9027 NAb:	negative	**not tested**
		Anti-PEG:	negative	negative
		Anti-PEG IgM:	negative	negative

EOT- End of Treatment
a Note: Subject (b) (6) , Subject (b) (6) , and Subject (b) (6) withdrew due to hypersensitivity reactions and had positive ADA results during the study. LoE was considered via post-infusion FVIII levels/recovery.
b For Subject (b) (6) , the event (drug hypersensitivity / anti-factor VIII antibody positive) actually occurred on ED 3 a few minutes following the third infusion.
c For Subject (b) (6) , the event (hypersensitivity) actually occurred on ED 4 following the fourth infusion.

Reviewer Comments: A total of 4 hypersensitivity reactions were noted in the pediatric patients. Three subjects were <6 years of age and one subject (3.75%) was 6 years old. The rate of hypersensitivity in children < 6 yrs was approximately 4 times higher than with adults. Similarly, the rate of hypersensitivity in children 6-<12 years of age is twice

the rate in adults. The rates, although observed in smaller sample sizes of pediatric subjects as compared to adult subjects, remains a safety concern in the reviewer's opinion. For a number of reasons, i.e., pre-disposition to hypersensitivity reactions with anti-PEG antibodies, presence of pre-treatment anti-PEG antibodies that may predispose patients to risks of hypersensitivity, additional concerns related to loss of efficacy, the reviewer concludes that the benefit risk assessment would not favor a labelling recommendation in children < 12 years of age. At present, screening of patients for anti-PEG antibodies is not feasible as diagnostic tests to reliably detect these antibodies are not available. Thus risk-reduction through screening is not a viable option. In addition, given the unexpectedly high rate of a potentially life-threatening condition such as hypersensitivity, a description of these risk in the Warnings and Precautions are insufficient to adequately address the safety concerns. Therefore, the reviewer does not recommend inclusion of subjects < 12 years in the indication.

Positive anti-study drug and/or anti PEG responses were detected in 6 subjects that were not associated with an AE. These positive results did not appear to have any clinical consequence, and none of positive results in these subjects was associated with a reported AE or loss of efficacy of the study drug. In 5 of these subjects, antibody was detected at screening and prior to first exposure to study drug. In 3 additional subjects only a positive test for the IgM anti-PEG assay was detected prior to first drug exposure, but was negative at Visit 3.

Reviewer Comments: It is unclear why there would be positive antibody prior to first exposures of the study drug. Subsequent testing revealed negative results. However, since some of the hypersensitivity reactions were observed in subjects who also developed anti-PEG antibodies, the relevance from a safety standpoint is unclear, i.e., whether development of anti-PEG antibodies predisposes patients to additional risks. The Applicant hypothesizes anti-PEG antibody development as possible mechanism that explains the hypersensitivity reaction.

6.3.12.6 Clinical Test Results

None of these shifts was considered clinically relevant in this subject population and none was reported as an AE by the investigator.

6.3.12.7 Dropouts and/or Discontinuations

As reported above.

6.3.13 Study Summary and Conclusions

Most AEs were mild or moderate (with the exception of hypersensitivity reactions) and not considered by the investigator to be related to the study drug. Across both age groups, the most common AEs referred to "infections and infestations" with the most common event being upper respiratory infection. There were 22 SAEs reported in 11 subjects. Three subjects (6 years of age and younger) experienced hypersensitivity reactions of moderate intensity (one after 1st dose, one after 4th dose, and one after 3rd dose) reported as SAEs. These three subjects dropped out of the study. Five subjects <6 years old dropped out of the study due to perceived loss of efficacy of the study drug. No subjects developed inhibitory antibodies to FVIII (≥0.6 BU/mL) during the study. Antibodies against the study drug and PEG and positive results for the specific IgM anti-PEG assay were observed. Due to these risks, the indication for subjects <12 years of age is not recommended.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1 Routine Prophylaxis

7.1.1 Methods of Integration

Data from the Main Study, Extension, and the Pediatric Study (Studies 13024 and 15912) are presented below. Integration of the Pediatric Study with the adult and adolescent study was not done based on the different study design. Integration is challenging, so the data are presented separately for each study, the goal being that the data from the different studies for the same indication are presented in the same section.

7.1.2 Demographics and Baseline Characteristics

Many of the patients from the main study continued treatment in the extension study; no relevant differences in population characteristics between the main and extension population were noted.

7.1.3 Subject Disposition

There were 134 subjects treated in the main study and 121 subjects who continued to the extension. 126 completed the main study and 37 subjects completed the extension.

7.1.4 Analysis of Primary Endpoint(s)

A markedly lower ABR was noticed for all prophylaxis regimens in comparison to the on-demand group. During the 26-week treatment period following Week 10, the median ABR was 2.09 when all prophylaxis groups were combined. Forty-two subjects (38.2%) had no bleeds during the 26-week period. By regimen, median ABRs were 4.11 and 1.93 in the 2x/week failed and forced groups, respectively, 1.93 in the every 5-day, and 3.85 in the every 7-day groups. By regimen, mean (SD) ABRs were 7.24(7.5) and 2.21 (2.72) in the 2x/week failed and forced groups, respectively, 3.3(4.26) in the every 5-day group, and 6.43 (10.04) in the every 7-day group. Thirty-eight percent (38%) of prophylaxis patients experienced no bleeds during the 26-week period. For patients in the on-demand group, median ABRs were 23.42during the Main study and 32.96 during the Extension.

For the 107 patients entering the extension study (adolescents/adults), the median ABR in the combined prophylaxis arms was 1.17. The median ABR by regimens were 2.21 in the 2x/week group, 1.17 in the every 5-day, 0.54 in the every 7-day, and 3.94 for patients with ‘variable frequency’ groups.

The median ABRs by age group were 2.47 (< 6 years) and 2.92 (6 to < 12 years). By prophylaxis regimen, median ABRs ranged from 1.86 (2x/week) to 5.65 (‘variable frequency’) in the younger group and from 0.99 (2x/week) to 10.62 (‘variable frequency’) in the older group.

7.1.5 Analysis of Secondary Endpoint(s)

N/A

7.1.6 Other Endpoints

N/A

7.1.7 Subpopulations

See discussion above regarding the pediatric subjects.

7.1.8 Persistence of Efficacy

The persistence of efficacy over time is anticipated with the study drug and has been demonstrated in the extension studies for a treatment period of up to almost 3 years.

7.1.9 Product-Product Interactions

N/A

7.1.10 Additional Efficacy Issues/Analyses

N/A

7.1.11 Efficacy Conclusions

Overall, prophylactic infusion with JIVI was effective for prevention of bleeds at dose intervals of 2x/week and every 5 days, as compared with a non-randomized control group of patients receiving on-demand treatment. JIVI was efficacious in subjects over 6 years of age. ABRs were higher in the <6 year age group. The ABR was also higher in the every 7-day dosing regimen in the main study. All adolescents were treated with a prophylaxis regimen and had a comparable ABR rate to those aged 18-34, but slightly higher compared to subjects over the age of 35.

7.2 Indication #2

Part B above discusses Perioperative Management. No other studies included these subjects.

7.2.1 Methods of Integration

N/A

7.2.2 Demographics and Baseline Characteristics

As above.

7.2.3 Subject Disposition

As above.

7.2.4 Analysis of Primary Endpoint(s)

N/A

7.2.5 Analysis of Secondary Endpoint(s)

N/A

7.2.6 Other Endpoints

N/A

7.2.7 Subpopulations

N/A

7.2.8 Persistence of Efficacy

N/A

7.2.9 Product-Product Interactions

N/A

7.2.10 Additional Efficacy Issues/Analyses

N/A

7.2.11 Efficacy Conclusions

As above.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

One hundred and forty-eight (148) adult and adolescent (12-18 years) subjects and 73 subjects < 12 years of age were evaluable for safety.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Main Study, Extension, Pediatric Study (Study 13024 and 15912)

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The demographics of the main study and extension study are comparable.

8.2.3 Categorization of Adverse Events

N/A

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

As the adult and pediatric studies were not the same study design, the main and extension was pooled. Further, the pediatric indication is not being sought by the applicant and due to safety concerns, not recommended.

8.4 Safety Results

8.4.1 Deaths

There were no deaths.

8.4.2 Nonfatal Serious Adverse Events

There was no 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 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).

8.4.3 Study Dropouts/Discontinuations

In the pediatric study, 11 subjects dropped out due to adverse events of hypersensitivity and loss of efficacy.

8.4.4 Common Adverse Events

The most frequently reported adverse reactions in PTPs ≥12 years of age were headache, cough, nausea, and fever.

8.4.5 Clinical Test Results

N/A

8.4.6 Systemic Adverse Events

N/A

8.4.7 Local Reactogenicity

N/A

8.4.8 Adverse Events of Special Interest

There were a total of 14 subjects who dropped out due to hypersensitivity and loss of efficacy. Six subjects had hypersensitivity reactions and 8 subjects had loss of efficacy. Twelve were <12 years and 2 were >18 years. Eleven of the 14 subjects had anti-PEG antibodies present.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

N/A

8.5.2 Time Dependency for Adverse Events

N/A

8.5.3 Product-Demographic Interactions

N/A

8.5.4 Product-Disease Interactions

N/A

8.5.5 Product-Product Interactions

N/A

8.5.6 Human Carcinogenicity

N/A

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

N/A

8.5.8 Immunogenicity (Safety)

The following table shows the number of subjects who tested positive for Anti-PEG antibodies.

Table 16: Subjects with positive antibodies

Type of antibody pre and post treatment*	**< 6 years (n=44) Positive/ tested (% positive)**	**6 to 12 years (n=29) Positive/ tested (% positive)**	**12 to < 18 years (n=13) Positive/teste d (% positive)**	**≥ 18 years (n= 121) Positive/teste d (% positive)**	**≥ 12 years (N = 134) Positive/ tested (% positive)**
Anti-PEG antibodies					
Pre treatment	1 / 44 (2.3 %)	2 / 29 (6.9%)	0 / 13	0 / 101	0 / 114 (0%)
Treatment emergent	7 / 43 (16.3%)	0 / 27 (0%)	0 / 12	6 / 121 (5.0%)	6 / 133 (4.5%)
Anti-PEG Ig M antibody					
Pre treatment	12 / 44 (27.3%)	1 / 29 (3.4%)	2 / 13 (15.4%)	1 / 101 (1.0%)	3 / 114 (2.6%)
Treatment emergent	4 / 32 (12.5%)	0 / 22 (0%)	1 / 10 (10.0%)	1 / 98 (1.0%)	2 / 108 (1.9%)
Anti-BAY-94-9027					
Pre treatment	5 / 44 (11.4%)	2 / 29 (6.9%)	1 / 13 (7.7%)	0 / 101	1 / 114 (0.9%)
Treatment emergent	6 / 39 (15.4%)	1 / 27 (3.7%)	0 / 11	5 / 121 (4.1%)	5 / 132 (3.8%)
Neutralizing antibody to BAY 94-9027					
Pre treatment	1 / 22 (4.5%)	0 / 5 (0%)	0	0	0 / 4 [b] (0%)
Treatment emergent	8 / 24 (33.3%)	0 / 3 (0%)	0	2	2 / 15 [b] (13.3%)
Number of patients who dropped out					
no. of subjects with HS/LoE	11	1	0	2	
no. with anti-PEG antibody	10 [a]	0	0	1	
Number of patients who dropped out					
due to HS	3	1	0	2	
due to clinical LoE	8	0	0	0	

Abbreviations: AB = antibody; HS = hypersensitivity; LoE = Loss of efficacy

a 6 subjects had anti-PEG IgM antibodies and/or positive NAb results at baseline with increasing titers during reaction in 4 subjects, and for 4 subjects anti-PEG IgM antibodies and/or NAb were treatment-emergent. For one subject no anti-drug antibody was detected

b including additional post-hoc analyses in selected patients

Source: Module 2.7.4, Section 3.2.2, Table 3-6 and Table 3-8; Module 2.7.4, Section 2.7.4.7 Appendix B; IR Response #41, Table 1 and Table 2

8.5.9 Person-to-Person Transmission, Shedding

N/A

8.6 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). Two (one adult subject and one pediatric subject) of the six subjects with hypersensitivity reactions did not develop anti-PEG antibodies. 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. Development of anti-PEG antibodies was the highest in children < 6 years of age, as well as the incidence of hypersensivity.

Loss of efficacy was associated with development of anti-PEG and NAB antibodies to BAY 94-9027 in the pediatric subjects, but not in adults.

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

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 outweighs the benefit to be approved for this age group. These risks will be addressed in the prescribing information.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

N/A

9.1.1 Human Reproduction and Pregnancy Data

N/A

9.1.2 Use During Lactation

N/A

9.1.3 Pediatric Use and PREA Considerations

The applicant completed efficacy and safety evaluations in pediatric studies across all age groups: 32 subjects 0-<6 years and 28 subjects 6-12 years. However, given the safety findings 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 and is not recommended. 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 and not warranted as the studies were already conducted.

9.1.4 Immunocompromised Patients

N/A

9.1.5 Geriatric Use

N/A

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

N/A

10. CONCLUSIONS

Overall, JIVI demonstrated efficacy in subjects over 6 years of age for on-demand treatment to control bleeding episodes, perioperative management of bleeding and routine prophylaxis. Due to high ABRs in the every 7-day dosing regimen and increased bleeding requiring increasing dose of frequency, this dosing regimen is not recommended. No deaths or treatment related FVIII inhibitors were observed in the safety evaluable pediatric, adolescent and adult subjects. The safety profile in pediatric subjects demonstrated hypersensitivity and antibody development which led to loss of efficacy in some pediatric subjects. Although hypersensitivity was seen in adults, the rate of this reaction was much lower compared to the pediatric subjects.

Due to the safety profile in pediatrics, labeling changes including communication in the Warnings and Precautions Sections will be updated, restricting the indication to adult and adolescent subjects.

JIVI is being approved for the following indications in adolescents and adults:
- On demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 17: Risk Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hemophilia A is a hereditary bleeding disorder characterized by recurrent bleeding, which if left untreated bleeds lead to chronic arthropathy, muscular atrophy and deformities. • Treatment of bleeds may delay these complications, but does not prevent it. • Primary prophylaxis with regular FVIII injections initiated at an early age is becoming the standard of care	• Hemophilia A is a hereditary, life-threatening disease • Hemophilia A can have a debilitating impact on physical and psychosocial well-being.
Clinical Benefit	• Three trials were submitted: 134 adult and adolescents subjects enrolled. Efficacy was demonstrated for the treatment of acute bleeds, perioperative management, and routine prophylaxis.	•The evidence for clinical benefit is shown in reduction of bleeds.
Risk	• The most substantial risks of treatment with JIVI are the development of FVIII inhibitors. • Serious adverse events of hypersensitivity, antibody development, and loss of efficacy occurred in the pediatric population	• JIVI was well tolerated in adolescents and adults.
Risk Management	• The most substantial risks of treatment with JIVI are the development of FVIII inhibitors. • Hypersensitivity and antibody development are risks to the pediatric population.	• The package insert is adequate to manage the risks.

11.2 Risk-Benefit Summary and Assessment

The benefits of JIVI include:

- On-demand JIVI is effective for treatment of and prevention of spontaneous or traumatic bleeding in patients with Hemophilia A
- JIVI is effective in the perioperative setting for reduction of bleeding during surgery.
- JIVI is effective in patients over (b) years of age.

The risks of JIVI include:

- Loss of Efficacy in patients <12 years of age, as reported in the pediatric trial due to hypersensitivity reactions and development of anti-PEG antibodies
- 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; however, given the risk of anti-PEG antibodies and hypersensitivity reactions noted in pediatric subjects less than 12 years of age, the risk outweighs the benefit, and approval in this age group is not recommended. These recommendations are consistent with the Applicant's requested indication.

11.3 Discussion of Regulatory Options

The available data support approval of the indication for on-demand treatment and control of bleeding episodes, peri-operative management, and routine prophylaxis for subjects over 12 years of age.

11.4 Recommendations on Regulatory Actions

An approval for the on-demand treatment and control of bleeding episodes, peri-operative management, and routine prophylaxis indication is recommended for adults and adolescents.

11.5 Labeling Review and Recommendations

The revised package insert (PI) was reviewed, commented, and revised by the appropriate discipline reviewers. APLB conducted its review from a promotional and comprehension perspective. Labeling issues have successfully been resolved with the applicant.

11.6 Recommendations on Postmarketing Actions

Bayer has proposed a phase IV interventional, open label, non-controlled study of at least 25 previously treated male patients $\geq$12 years of age with severe hemophilia A. This study is being undertaken to meet the target of 200 patients achieving 100 exposure days, as required by the EMA, but not FDA.

No PMR or PMC studies are requested at this time.