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Application Type	Original BLA
STN	125661/0
CBER Received Date	August 30, 2017
PDUFA Goal Date	August 30, 2018
Division / Office	OTAT
Committee Chair	Zuben Sauna, Ph.D.
Clinical Reviewer(s)	Megha Kaushal, M.D.
Project Manager	Candace Jarvis, M.S. Olukayode Owosela, M.S.
Reviewer Name(s)	Lin Huo, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Renée C. Rees, Ph.D., Team Leader, Therapeutics Evaluation Branch
	Boguang Zhen, Ph.D., Branch Chief, Therapeutics Evaluation Branch
	John Scott, Ph.D., Director, Division of Biostatistics
Applicant	Bayer Healthcare, LLC
Established Name	Antihemophilic Factor (Recombinant), PEGylated
(Proposed) Trade Name	JIVI
Dosage Form(s) and Route(s) of Administration	Lyophilized powder/ Intravenous
Dosing Regimen	45-60 IU/kg every 5 days, (b) (4) or 30-40 IU/kg 2 times per week
Indication(s) and Intended Population(s)	For use in previously treated adults and adolescents (12 years of age and older) with hemophilia A for (i) on-demand treatment and control of bleeding episodes, (ii) perioperative management of bleeding, and (iii) routine prophylaxis to reduce the frequency of bleeding episodes.

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GLOSSARY

ABR	Annualized Bleeding Rate
AE	Adverse Event
AUC	Area Under the Curve
BDD	B-Domain Deleted
BLA	Biologics License Application
CRF	Case Report Form
CSR	Clinical Study Report
ED	Exposure Day
EPD	Electronic Patient Diary
FDA	Food and Drug Administration
HIV	Human Immunodeficiency Virus
IND	Investigational New Drug
ITT	Intent-to-treat
IU	International Unit
IV	Intravenous
kDa	Kilodalton
PEG	Polyethylene Glycol
PK	Pharmacokinetic
PTPs	Previously Treated Patients
PUPs	Previously Untreated Patients
rFVIII	Recombinant human factor VIII
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
$t_{1/2}$	half-life
US	United States

1. EXECUTIVE SUMMARY

This is an original Biologics License Application (BLA) for the applicant's recombinant human DNA sequence derived, B domain Deleted (BDD) Factor VIII concentrate product with the trade name of JIVI (also referred to as BAY94-9027 in this review). JIVI was developed as long-acting recombinant FVIII (rFVIII) with increased area under the curve (AUC) and an extended half-life ($t_{1/2}$) compared to standard rFVIII products through reduced clearance from plasma by PEGylation while retaining the normal activity of the FVIII molecule. It offers a new treatment option for hemophilia A patients, with less frequent infusions for effective prophylaxis as compared to approved unmodified FVIII replacement products.

JIVI is proposed for the indication of on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis treatment to reduce the frequency of bleeding episodes in previously treated adults and adolescents (12 years of age and older) with hemophilia A. The PROTECT VIII study is considered the pivotal study for the submission.

PROTECT VIII was a phase 2/3 multicenter, open-label, uncontrolled, partially randomized study to demonstrate efficacy and safety of treatment with JIVI for prophylaxis, treatment of bleeds, and surgeries in previously treated patients (PTPs) (≥150 exposure days [EDs]), 12 to 65 years of age, with severe hemophilia A. Part A of the study evaluated the PK (single dose of 60 international unit [IU]/kg), safety and efficacy of JIVI for on demand treatment and routine prophylaxis. Safety and efficacy of JIVI in hemostasis during major surgical procedures was evaluated in Part B. An optional extension was offered to subjects who had completed Part A to accumulate at least 100 EDs for the collection of additional safety and efficacy data, including surgery.

The primary efficacy variable in Part A was the annualized bleeding rate (ABR) of total bleeds, and the primary analysis was conducted in 132 subjects (on-demand: 20 subjects; prophylaxis: 112 subjects) aged 12 to 62 years in the intent-to-treat (ITT) population. For all **prophylaxis** regimens combined, the ABR (± SD) of total bleeds during the 26-week main efficacy assessment period was 4.9 ± 7.5 bleeds (median: 2.1 bleeds). By regimen, ABRs were 7.2 ± 7.5 (N=13; median: 4.1 bleeds) and 2.2 ± 2.7 (N=11; median:1.9 bleeds) in the 2x/week "failed" and "forced" groups, respectively; 3.3 ± 4.3 (N=43; median: 1.9 bleeds) in the every 5-day; and 6.4 ± 10.0 (N=43; median: 3.9 bleeds) in the every 7-day groups. For the **on-demand** group, the ABR of total bleeds during the 36-week treatment period was 28.8 ± 17.8 bleeds (N=20; median: 24.1 bleeds).

For the 107 subjects entering the **extension study**, the ABR in the combined prophylaxis groups was 3.8 ± 5.9 (median: 1.2 bleeds). The ABRs by regimen were 4.0 ±4.9 (N=24; median: 2.2 bleeds) in the 2x/week group; 4.4 ± 6.8 (N=37; median: 1.2 bleeds) in the every 5-day; 1.6 ± 3.7 (N=29; median: 0.5 bleeds) in the every 7-day; and 5.8 ± 7.1 (N=17; median: 3.9 bleeds) for the subjects with "variable frequency" groups.

The **treatment response** was assessed as "good" or "excellent" in 82.6% (all prophylaxis regimens combined) and 65.9% (on-demand group) of the bleeding

episodes in Part A, and 86.5% (all prophylaxis regimens combined) and 70.4% (on-demand group) in the extension study, respectively.

Twenty major and 34 minor **surgeries** were performed during part B and the extension part of the study. The hemostatic control during major and minor surgeries was "good" or "excellent" in all cases.

A total of 33 PTPs experienced at least one treatment-emergent serious adverse event (SAE) in the study. Four subjects had SAEs classified as related to JIVI and three subjects discontinued due to SAEs. In Part B of the study, two cases of low titer FVIII inhibitors were reported as drug-related SAEs, but one had a pre-existing low-titer FVIII inhibitor. No subjects died during the study.

I verified the primary and some secondary efficacy results for the PROTECT VIII study. No discrepancies were found. The statistical evidence supports approval of the applicant's proposed indications for JIVI in BLA 125661/0.

2. CLINICAL AND REGULATORY BACKGROUND

JIVI is a recombinant BDD human coagulation FVIII variant which is site specifically conjugated with a single maleimide-derivatized 60 kilodalton (kDa) branched polyethylene glycol (PEG) (two 30 kDa PEG) at the cysteine (b) (4) (amino acid 1840 in the full length FVIII sequence). It is supplied as lyophilized powder in sterile glass vials and is reconstituted with 2.5 mL sterile water for injection. It will be available in five vial sizes (nominal (b) (4) 500 IU, 1000 IU, 2,000 IU, and 3,000 IU per chromogenic substrate assay).

JIVI has the same mechanism of action as unmodified FVIII. The site specific PEGylation of JIVI results in an increased AUC and extended $t_{1/2}$ through reduced clearance from plasma.

2.1 Disease or Health-Related Condition(s) Studied

Prevalence

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

Clinical presentation

Hemophilia A is usually diagnosed by measuring FVIII clotting activity (FVIII:C) level in the plasma of a patient. There is a direct correlation between FVIII activity levels and clinical manifestations. Hemophilia A is defined as severe if the plasma FVIII:C level (measured as IU/dL) is <1%, moderate if it is between 1% and 5%, and mild if it is between > 5% and 40% of normal.

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

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

Standard treatment for these patients is the replacement of the missing protein by intravenous infusion of either plasma-derived FVIII or rFVIII. This increases the plasma concentrations of FVIII, thereby enabling a temporary correction of the factor deficiency and reversal of the bleeding tendencies. Until recently, the treatment regimens have been either **on-demand** therapy (given when a bleed occurs) or **prophylaxis** (which consists of regular infusion of FVIII given every 2 to 3 days to prevent bleeding). Products with an extended $t_{1/2}$ and less frequent infusion requirement have been approved recently in the United States (US), Canada, Europe, Australia, and other countries worldwide (such as Elocta®, Eloctate®, Adynovate®) which provide new treatment options with dosing intervals of 3 to 5 days.

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

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

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

JIVI has been developed under the Investigational New Drug (IND) application 14369 using a developmental name of BAY 94-9027. There were multiple pre-submission interactions between the Food and Drug Administration (FDA) and the applicant. A summary of regulatory history with statistical implications is given below:

- A type C meeting was held on March 5, 2009 to seek FDA's feedback on the development plans to support clinical trials for BAY 94-9027. FDA advised that 1) the duration of pivotal study be 12 months to evaluate the ABR between prophylaxis and on-demand, due to concern on bleeding seasonality; 2) ten surgeries should occur in at least ten subjects to support the surgical indication; 3) Kogenate FS be used as the comparator in a Phase 1 PK study. No comparator needed for the Phase 2/3 study. After the discussion, FDA agreed that the Phase 2/3 program consisting of a single study for 26 weeks was appropriate to support a marketing application. Additional data from the interim extension study would be included in the BLA which would cover a total treatment time of >2 years for most subjects in the extension. The applicant acknowledged FDA's other comments and implemented the study plan.
- On November 8, 2016, FDA provided comments to the applicant's pre-BLA meeting questions. FDA recommended the applicant specify the statistical methods for the study and clarify how they would determine the efficacy of each dosing regimen in the pre-BLA package. The applicant provided the justification of using a negative binomial model post hoc and clarified their intent not to assess a difference across different dosing regimens. The applicant submitted the statistical analysis plan with the pre-BLA package.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

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

5.1 Review Strategy

The clinical development program of BAY 94-9027 consists of three studies: a Phase 1 First-in-Man study, and two phase 2/3 studies (PROTECT VIII and PROTECT Kids).

Phase 1 study was a multi-center, non-randomized, open label, parallel group study to evaluate the PK and safety profile of BAY 94-9027 following single and multiple dose administration in two cohorts of previously treated male subjects (≥18 and ≤ 65 years of age, at least 150 EDs prior to study) with severe hemophilia (FVIII level < 1%). The study included a PK comparison to Kogenate FS. The data from this phase 1 study were used to define the dosage regimen for subsequent studies and clinical use.

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

PROTECT VIII was a phase 2/3 multicenter, open-label, uncontrolled, partially randomized study to demonstrate efficacy and safety of treatment with BAY 94-9027 for prophylaxis, treatment of bleeds, and surgeries in PTPs (at least 150 EDs with previous FVIII products), 12 to 65 years of age, with severe hemophilia A (< 1% FVIII:C). The study consists of part A, part B, and an extension part.

Parts A and B are considered the main study and are complete. At the time of the BLA submission, the extension study was ongoing and an interim analysis of efficacy and safety data as of January 9, 2015 was submitted. The main study analysis and the interim analysis of the extension study will be reviewed together in section 6. In addition, a summary of preliminary efficacy data from the ongoing extension study as of February 15, 2017 was submitted (these data are not included in the labelling) and will also be reviewed in section 6.

PROTECT Kids was a phase 3 multicenter, open-label, uncontrolled study to assess the PK, efficacy, and safety of treatment with BAY 94-9027 for prophylaxis and treatment of bleeds in previously treated children with severe hemophilia A (< 12 years of age and at least 50 EDs with previous FVIII products).

Due to the high rate of immune response to PEG in pediatric subjects < 6 years of age, which resulted in loss of efficacy and/or hypersensitivity in approximately 25% of the subjects, a favorable benefit/risk profile for pediatric subjects cannot be established in this age group. Therefore, the applicant decided to exclude this subject group from the indication treatment population. The results of this study are not covered in this review.

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

- Original submission under BLA 125661/0
  - Module 1.6: Meetings

- Module 1.14: Labeling
- Module 2.2: Introduction
- Module 2.5: Clinical Overview
- Module 2.7: Clinical Summary
- Module 5.3.5.2: Clinical Study Report (CSR) for BAY 94-9027, Statistical Analysis Plans (SAPs) and tabulation data
  - The main CSR (1305 pages), Version 3.0, dated July 6, 2017 with 189-page main text.
  - The main Protocol (245 pages), Amendment 11, dated March 25, 2014.
  - The main SAP (246 pages), Version 3.0, dated January 13, 2014.
  - The extension CSR (821 pages), Version 2.0, dated May 8, 2017 with 115-page main text.
  - The extension Protocol (259 pages), Amendment 5, dated December 2, 2014.
  - The extension SAP (199 pages), Version 6.0, dated August 7, 2015.

- BLA amendment 125661/23, Module 1.2, Response to FDA information request #18
- BLA amendment 125661/27, Module 1.2, Response to FDA information request #22
- BLA amendment 125661/41, Module 1.2, Response to FDA information request #31

5.3 Table of Studies/Clinical Trials

The clinical development program of BAY 94-9027 consists of three studies. An overview of these studies is provided in Table 1.

Table 1. Overview of BAY 94-9027 Clinical Studies Contributing to the Clinical Development Program

Study or study part	Number of PTPs treated	Age (according to protocol)	Treatment	Duration
Phase 1 study	14	≥ 18 years	25 IU/kg 2x/week 60 IU kg every 7 days	8 weeks
PROTECT VIII				
Main study, Part A	134 (total) On-demand: 20 Prophylaxis: 114	12 to 65 years	On-demand: Up to 60 IU/kg per infusion Prophylaxis: Run-in: first 10 weeks (all subjects) 2x/week with 25 IU/kg; Week 10 to 26: 2x/week: 30-40 IU/kg Every 5 days: 45-60 IU/kg Every 7 days: 60 IU/kg	10 weeks plus 26 weeks
Main study, Part B (surgeries)	17	12 to 65 years	Up to 60 IU/kg per infusion	Up to 3 weeks
Interim Extension (9 Jan 2015)	121	12 to 65 years	same as main study	≥ 100 EDs (total), ongoing
PROTECT Kids				
Main study	61	0 to < 12 years	2x/week: 25-60 IU/kg Every 5 days: 45-60 IU/kg Every 7 days: 60 IU/kg	≥ 50 EDs or 6 months
Part 2	12	0 to < 6 years	2x/week: 25-60 IU/kg	12 weeks
extension	59 (preliminary)	0 to < 12 years	same as main study	≥ 100 EDs (total), ongoing

Source BLA 125661/0; Module 2.5 Clinical overview, Table 1-1.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 PROTECT VIII

PROTECT VIII study was titled "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". Parts A and B are considered the main study and are complete. An optional extension of the main study was available to subjects who completed Part A and was still ongoing at the time of the BLA submission.

6.1.1 Objectives (Primary, Secondary, etc.)

Part A

Primary objective:

- To assess the efficacy of BAY 94-9027 in prevention and treatment of bleeding at different infusion schedules

Secondary objectives:

- To evaluate the subject's assessment of response to treatment
- To demonstrate the safety and tolerability of BAY 94-9027 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 BAY 94-9027
- To assess treatment satisfaction with BAY 94-9027 and its impact on quality-of-life, work productivity and pain as reported by the subjects

Part A Extension

- To assess the long-term safety of BAY 94-9027 over at least 100 accumulated EDs (main study plus extension)

Part B and Extension

- To assess the safety and efficacy of BAY 94-9027 in the prevention of bleeding during major surgical procedures

6.1.2 Design Overview

This multicenter, open-label, uncontrolled study to evaluate the PK, safety, and efficacy of treatment with BAY 94-9027 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) is comprised of the following parts:

Part A On-demand and prophylactic treatment with BAY 94-9027

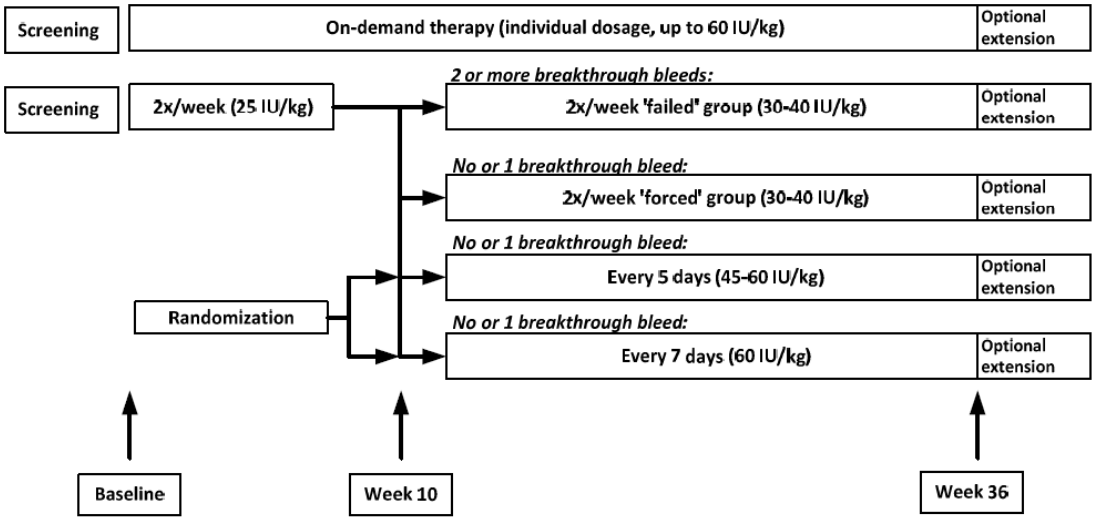
Part A (see Figure 1) was to assess the PK, efficacy, and safety of BAY 94-9027 for prophylaxis using different regimens and treatment of bleeding. Part A was to include on-demand and prophylactic treatment arms; subjects were to be asked to identify their preferred treatment (on-demand or prophylaxis) when consent was signed. In Part A, all subjects were to receive treatment for a total of 36 weeks. All subjects entering the prophylaxis arm were to start with 2x/week infusions at 25 IU/kg (Week 0 to 10). Following a clinical assessment at Week 10, subjects with less than two spontaneous (joint/muscle) bleeds in Weeks 0 to 10 were to be randomized 1:1 to either an every 5-day or every 7-day prophylactic regimen for an additional 26 weeks. Subjects with at least two spontaneous bleeds during the first 10 weeks (defined as 2x/week "failed") or those who qualified for randomization after the randomization

arms had been filled (due to capping) were to remain in the 2x/week arm (defined as "forced") for Weeks 10 to 36.

Occasional extra infusions prior to activities or events that were expected to result in an increased risk of bleeding were to be permitted. Subjects who experienced an unacceptable increase in their number of bleeding events could increase their dose or shift to a regimen with increased frequency according to predefined rules. The period from Week 10 to 36 was defined as the main efficacy period for prophylaxis treatment.

Subjects requiring minor surgery during the trial were to be treated with BAY 94-9027. Minor surgery was defined as any surgical procedure that did not meet the definition of major, and may have included simple dental extractions, incision and drainage of abscess, or simple excisions.

Figure 1. Study Design of Part A - Main study



Source: Original from BLA 125661/0; Module 2.5 Clinical overview, Figure 1-1.

Part B Major surgery using BAY 94-9027

Part B was an open label, non-controlled, single arm study to assess the safety and efficacy of BAY 94-9027 in hemostasis during major surgical procedures. It 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. Subjects may have undergone surgery more than once as part of their participation.

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).

Subjects who underwent major surgery were to receive BAY 94-9027 for pre-surgical PK measurements followed by treatment with the study drug during their hospital stay and up to time of discharge, for a period not exceeding 3 weeks.

Subjects who were already participating in Part A were to continue treatment with BAY 94-9027 as per treatment assignment. Subjects who participated only in Part B were to be considered as having completed the study at the time of the postsurgical visit.

Extension

An optional extension was offered to subjects who had completed Part A to accumulate at least 100 EDs, or until marketing authorization of the drug for the collection of additional safety and efficacy data, including surgery. Subjects had the option to switch treatment regimen at the start of the extension study as well as at any time during extension. The extension of Part B, i.e., continuation of the surgery part, was offered to subjects enrolled in the Part A extension who required a major surgical procedure.

6.1.3 Population

Subject eligibility criteria:

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
3. Previously treated with FVIII concentrate(s) (plasma derived or recombinant) for a minimum of 150 EDs
4. Immunocompetent. If human immunodeficiency virus (HIV) positive, CD4+ lymphocyte count >200/mm^3
5. Willingness and ability of subjects and/or parents to complete training in the use of the Electronic Patient Diary (EPD) and to document bleeds and infusions during the study
6. Written informed consent from subject or legal representative; assent from subject when appropriate.

6.1.4 Study Treatments

Prophylaxis treatment

Test drug:	BAY 94-9027
Dosage:	25-60 IU/kg (rounded to the nearest vial size), maximum 6,000 IU
Route of administration:	intravenous (IV) infusion over 1 to 15 min to total volume

2x/week treatment arm: All subjects enrolled in the prophylaxis arm began treatment with 2x/week infusion at a dose of 25 IU/kg. Subjects who remained in this arm increased their dose to 30 to 40 IU/kg either at Week 10, or at any time after ineligibility for randomization had been determined.
Subjects were infused on the same days each week to provide balanced intervals between infusions (e.g., Monday and Thursday, Tuesday and Friday, etc.).

Every 5 days treatment arm: Subjects randomized to the every 5-day treatment arm were began treatment with 45 IU/kg/dose infused every 5 days. If in the subject's and investigator's assessment the dose could not provide sufficient protection against bleeds, the dose could be increased to 45 to 60 IU/kg/dose (maximum of 6000 IU).

Every 7 days treatment arm: Subjects on the every 7-day arm were treated with a fixed dose of 60 IU/kg (maximum 6,000 IU). Subjects were advised to pick the day of the week for infusion which correlated with their peak physical activity.

On-demand treatment

The dosage required to treat bleeding events for both the on-demand and prophylaxis treatment arms was determined at the investigators' discretion, according to the type, location and severity of the bleeding event.

Treatment during surgery

Test drug:	BAY 94-9027
Dosage:	Loading dose of 50 IU/kg (or as determined by individual PK) given < 60 min before start of procedure; 15 to 50 IU/kg (rounded to full vial) repeated as indicated.
Route of administration:	IV infusion over 1 to 15 min
Duration:	As needed

Treatment during the Part A extension phase

Subjects receiving prophylaxis in the extension received either the every 7-day, every 5-day, or 2x/week regimen using a dosage in the range specified for that dosing frequency during the main study. Subjects receiving on-demand treatment in the extension were permitted to change to one of the prophylaxis regimens.

6.1.6 Sites and Centers

Part A was conducted at 58 centers that enrolled 134 subjects across 19 countries (number of subjects in brackets): Austria (5), Belgium (2), Canada (1), Colombia (5), Germany (4), Denmark (5), France (6), United Kingdom (8), Israel (16), Italy (5), Japan (11), South Korea (8), Netherlands (7), Norway (3), Poland (3), Singapore (9), Turkey (5), Taiwan (4), and the US (27).

The subjects participating in Part B were from the following countries (number of subjects in brackets): Austria (1), France (1), United Kingdom (1), Israel (1), Italy (3), Netherlands (1), Romania (2), Turkey (1), Taiwan (1), and the US (4).

The Part A extension of the main trial was conducted at 52 study centers that enrolled 116 subjects in 18 countries (number of subjects in brackets): 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 US (24).

6.1.8 Endpoints and Criteria for Study Success

Part A

Primary efficacy variable was the ABR of total bleeds (sum of spontaneous bleeds and trauma bleeds).

Subjects with less than nine total bleeds per year who did not increase the dosing frequency or drop out were considered responders. The responder rate was to be evaluated in subjects who were enrolled in the prophylactic treatment arm for an evaluation period starting from Week 10 to Week 36 while the subject adhered to the initially randomized dosing frequency. If a minimum response rate of 50% for each treatment arm was achieved, efficacy would be determined by comparison of bleeding rates to the on-demand treatment arm. The 50% responder rate is an arbitrary cut-off below which the corresponding treatment would be considered ineffective.

Secondary efficacy variables include:

- Subject or investigator assessment of response to treatment of a bleed, as excellent, good, moderate, or poor, and defined as:
  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.
- Description of bleeding according to 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
- FVIII usage expressed as number of infusions, number of prophylaxis infusions, and number of infusions to treat breakthrough bleeds.
- FVIII recovery values
- (Prophylaxis subjects only) Proportion of prophylaxis infusion that were followed by a bleed within 48, 72, 96, 120, 144 and 168 hours
- (Prophylaxis subjects only) Number of subjects requiring dose escalation
- (Prophylaxis subjects only) Proportion of responders

Part B

- Investigator's assessment of response to treatment, described as excellent, good, moderate, or poor, and defined as:
  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 bleeding, but no need to change therapeutic regimen
  Poor: Inadequate therapeutic response, change in therapeutic regimen required
- Blood loss
- Need for additional hemostatic medication, including blood products
- Units of blood transfused
- Hemostatic-related surgical complications
- Change in hemoglobin/hematocrit
- rFVIII usage

Extension

- Frequency of inhibitor development

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis populations

- **Safety Population** – all subjects enrolled into the study who received at least one dose of study drug. The safety population was to be used for all safety analyses.
- **Intent-to-Treat (ITT) Population** –all safety subjects who had infusion/bleeding data from EPD and Case Report Form (CRF). The ITT population was to be used for the primary efficacy analysis.

Subgroup analyses

The subgroup analyses planned for the primary efficacy variable included:

- Baseline joint status (has target joint or not)
- Age group 1 (<18 years, >=18 years)
- Age group 2 (<18 years, 18-<35 years, >=35 years)
- Race (White, Black, Asian, Other)
- Region (North America, Europe, Israel, Asia, Central and South American)
- BMI (<25 kg/m^2, 25 kg/m^2-<30 kg/m^2, ≥30 kg/m^2)
- Prior treatment (on-demand, prophylaxis)
- Gilbert score

Sample size determination

No formal statistical samples size estimates were performed.

According to the guideline "Note for guidance on the clinical investigation of recombinant and plasma factor VIII products" EMA/CHMP/BPWP/144533/2009, at least 50 PTPs ≥ 12 years of age were to be followed for at least 50 EDs. Total sample size of the prophylaxis treatment group was picked to ensure that at least 50 subjects (including at least 12 subjects between 12 and < 18 years of age) enrolled in the combined 2x/week and every 5 days treatment groups would accumulate at least 50 EDs. Twenty subjects enrolled in the on-demand treatment group were to provide assessment of the efficacy of BAY 94-9027 for the treatment of acute bleeding events, and in the assessment of safety/immunogenicity, and for comparison of bleeding rates.

During the randomization between the every 5-day and the every 7-day regimens, there was a cap (N=43) for each group. Subjects who qualified for randomization after the randomization arms had been closed due to capping had to continue treatment in the 2x/week arm.

Handling of missing data

All missing or partial data were to be presented as missing in the subject data listings as they were recorded on the CRF. The following imputation rules were to be implemented so as not to exclude subjects from statistical analyses due to missing or incomplete data:

- If a bleed has a missing date/time, then the date of the associated infusion will be used as the bleed date/time. If the infusion for a bleed has a missing date/time, then the associated bleed will be used to determine the infusion date/time.
- For subjects in both the prophylaxis and on-demand treatment arm, if there was no information regarding the adverse event (AE) start day, or there was partial

information that AE started after treatment, the missing AE start day was to be imputed as first day of dosing in the clinic at Visit 2. For subjects who participate in Part B only, the missing AE start day was to be imputed as the day of first PK collection. If there was information that AE occurred before the treatment, the date of the day prior to the treatment day was to be used. Missing end date for an AE was not to be imputed.

Statistical methodology

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

For all subjects, the evaluation period started at Week 0 when first dose of study drug was administered. For on-demand subjects, the evaluation period was weeks 0-36. For prophylaxis subjects, there were multiple evaluation periods: Weeks 0-10, Weeks 10-36, and Weeks 0-36.

The number of infusions used to treat a bleed was to be summarized, including the proportion of bleeds controlled by one or two infusions. The subject and investigator assessment of adequacy of hemostasis for treatment of a bleed as excellent, good, moderate and poor was to be summarized.

In Part B, study drug and blood product treatments used during surgery were to be summarized and listed for these subjects, as well as blood loss at surgery and the assessment of hemostasis during the peri-surgical period.

The following parameters were to be evaluated for each subject, and for each treatment arm:

Total bleeds

Total bleeds = spontaneous bleeds + trauma bleeds

Rescue bleed

Subjects in the every 5-day and every 7-day treatment arms who experienced what the subject considered to be an unacceptable increase in bleeding frequency, and could result in their decision to leave the study, had the option of a one-time change in dose frequency. A subject who has the one-time change in dose frequency is regarded as rescued. A rescue bleed is a bleed that occurs after the dose frequency is increased. However, because some subjects changed their dose frequency in anticipation of going into the extension part, change in dose frequency that occurred within 7 days of Week 36 in the main study did not cause the subject to be considered as rescued.

Annualized number of bleeds

$$Annualized\ number\ of\ bleeds = \frac{\#\ of\ bleeds * 365.25 * 24 * 60}{period}$$

Period is defined as the number of minutes calculated from the date and time of the beginning of the evaluation period to the date and time of the end of the evaluation period.

Safety data were to be summarized. Laboratory findings, adverse events, concomitant medications, vital signs, and medical history data were to be provided in subject listings.

In a *post-hoc* analysis using a negative binomial regression model, ABRs were compared between the on-demand group (Week 0 to 36) and the different prophylaxis regimens (Week 10 to 36). The negative binomial model was also used for comparing ABRs in the every 5-day and every 7-day (completers) regimens, with the 2x/week "forced" regimen.

Sensitivity analysis

Sensitivity analyses were planned by defining responders as subjects with less than 3, 5, 7, or 11 bleeds per year who did not increase their dosing frequency, and then calculating the responder rate accordingly to see if the study goal of a 50% responder rate was still achieved under this definition.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Part A and Extension

A summary of the Part A analysis sets for the main and interim extension study is given in Table 2.

Table 2. Analysis sets of PROTECT VIII Main and Interim Extension study (Part A)

		Main Study	Interim Extension (cut-off: 9 Jan 2015)
Enrolled		149	121
Screening failure		15	-
Assigned to treatment		134	-
Not treated		0	-
Treated	On-demand	20	14
	Prophylaxis	114	107
	Total	**134**	**121**
Discontinued	On-demand	2	0
	Prophylaxis	6	6
	Total	**8**	**6**
ITT	On-demand	20	14
	Prophylaxis	112	107
	Total	**132**	**121**
Safety set	On-demand	20	14
	Prophylaxis	114	107
	Total	**134**	**121**

Source: Adapted from BLA 125661/0; Module 2.7.3 Summary of Clinical Efficacy, Tables 3-1 and 3-2

Two subjects discontinued after a single dose of study drug and were excluded from the ITT population because no efficacy data for these subjects were available.

Subsequent to the database lock of the main study, three additional bleeds were identified as a consequence of subjects continuing in the extension or as part of internal monitoring quality assessment.

- Two bleeding events (subject (b) (6) in the on-demand group, subject (b) (6) in the prophylaxis group), which were not documented in the

EPDs, were identified in the subjects' medical records at the investigator's sites after database lock and after the subjects had left the study, as part of the internal monitoring quality assessment.

- One bleed (subject (b) (6) in the on-demand group) was retrospectively entered in the EPD by the subject several months after the event occurred, and after the subject had completed the main study and entered the extension study.

The applicant performed a thorough assessment of these three events and determined that they did not affect the outcome of the study: two bleeds occurred in on-demand subjects and do not affect any outcome related to the primary endpoint of ABR during prophylaxis; one bleed in a prophylaxis subject occurred during the run-in period and does not affect the primary outcome parameter, the ABR during the main efficacy period of Weeks 10-36. Therefore, these three bleeding events were documented in the CSR errata section but not included in the efficacy analyses of the study at the time of the BLA submission.

Reviewer Comment: During the review of the study, both the clinical reviewer and I believe these three bleeding events should be included in the efficacy analyses to accurately reflect the study data. Per FDA's request, the applicant updated the affected efficacy results in the CSR and the package insert through manual calculation with validation documentation; the database was not unlocked to do these analyses. All the results reviewed in this memo are updated results including these three bleeding events.

Part B
A total of 17 subjects (Part B ITT population) were included in the efficacy assessment of BAY 94-9027 during 20 major surgeries.

6.1.10.1.1 Demographics
Part A and Extension
In Part A of the main study, more than half of the subjects were White and approximately a quarter were Asian in the on-demand and prophylaxis groups. Subjects had a median age of 48 years (range: 22 to 61 years) in the on-demand group and 33 years in the prophylaxis group (range: 12 to 62 years). Three quarters of subjects in the on-demand group were ≥ 35 years, whereas less than half of the prophylaxis population were in this age group. Medians of body weight, height, and BMI were comparable between the groups (on-demand group: 69.8 kg, 171.8 cm, and 24.6 kg/m^2; prophylaxis group: 75.0 kg, 175.2 cm, and 24.0 kg/m^2).

Because many of the subjects from the main study continued treatment in the extension study, no relevant differences in population characteristics between the main and extension population were noted (see Table 3). No clinically relevant differences in demographic characteristics were noticed between the different prophylaxis arms in both Part A and the extension study. A summary of the demographic and other baseline characteristics is shown in Table 3.

Table 3. Demographic and other baseline characteristics (Part A, Safety population)

	Main study		Interim Extension	
	On-demand group (N = 20)	Prophylaxis group (N = 112) [a, b]	On-demand group (N = 14)	Prophylaxis group (N = 107) [a]
Sex [n (%)]				
Male	20 (100.0%)	112 (100.0%)	14 (100.0%)	107 (100%)
Race/ethnicity				
White	11 (55.0%)	75 (67.0%)	7 (50.0%)	71 (66.4%)
Black or African American	1 (5.0%)	4 (3.6%)	1 (7.1%)	4 (3.7%)
Asian	5 (25.0%)	27 (24.1%)	5 (35.7%)	25 (23.4%)
Not reported	3 (15.0%)	6 (5.4%)	1 (7.1%)	7 (6.5%)
Age [years]				
Mean ± SD	44.8 ± 13.5	34.6 ± 12.9	43.5 ± 14.1	34.8 ± 13.2
Median	48.0	33.0	43.5	33.0
[Min; Max]	[22; 61]	[12; 62]	[22; 61]	[12; 62]
Age group [n (%)]				
<18 years	0 (0%)	12 (10.7%)	0 (0%)	12 (11.2%)
18 to 34 years	5 (25.0%)	47 (42.0%)	4 (28.6%)	43 (40.2%)
≥ 35 years	15 (75.0%)	53 (47.3%)	10 (71.4%)	52 (48.6%)
Baseline weight [kg]				
Mean ± SD	71.8 ± 13.3	76.2 ± 16.8	75.4 ± 13.4	75.4 ± 16.7
Median	69.8	75.0	74.5	72.2
[Min; Max]	[55; 100]	[37; 126]	[57; 100]	[37; 126]
Baseline height [cm]				
Mean ± SD	171.5 ± 7.2	175.2 ± 8.0	172.9 ± 7.2	174.7 ± 8.1
Median	171.8	175.2	174.7	175.0
[Min; Max]	[156; 182]	[155; 192]	[156; 182]	[155; 192]
Baseline BMI [kg/m^2]				
Mean ± SD	24.4 ± 4.3	24.7 ± 4.7	25.2 ± 4.2	24.6 ± 4.8
Median	24.6	24.0	26.0	23.9
[Min; Max]	[19; 31]	[14; 42]	[19; 31]	[14; 42]

Demographic data is based on the values collected at screening visit of Part A.
a The prophylaxis group comprises all prophylaxis regimens.
b Of these 112, 2 patients dropped out during the run-in phase prior to Week 10.

Source: BLA 125661/0; Module 2.7.3 Summary of Clinical Efficacy, Table 3-7

Part B

The majority of subjects were White (15 out of 17 subjects, 88.2%) and all were male. Subjects had a median age of 37 years (range: 13 to 61 years), a median weight of 77.7 kg (range: 46 to 99 kg), a median height of 172.7 cm (range: 158 to 191 cm), and a median BMI of 25.3 kg/m^2 (range: 18 to 31 kg/m^2).

6.1.10.1.2 Disease Characterization of the Enrolled Population

Part A and Extension

In the main study, the median number of bleeds during the 12 months preceding the study was 22 (range: 6 to 64 bleeds) in the on-demand group and 7 (0 to 98 bleeds) in the prophylaxis group. Most subjects in either treatment group had target joint bleeds (on-demand group: 80% or 16 subjects; prophylaxis group: 72.3% or 81 subjects). The median number of target joint bleeds per subject was 2 (range: 0 to 8) in the on-demand group and 1 (range: 0 to 6) in the prophylaxis group. One subject in the on-demand group had a history of FVIII inhibitors, and for two subjects each in the on-demand and prophylaxis groups, a family history of FVIII inhibitors was reported. Information on gene mutation was available for 8 subjects in the on-demand group and

55 subjects in the prophylaxis group. Approximately 40% of the subjects in the prophylaxis group had an intron 22 inversion, representing the expected distribution in the study population. Disease characteristics for subjects entering the extension study were similar.

No clinically relevant differences in disease characteristics were noticed between the different prophylaxis arms except for the number of bleeds during the 12 months preceding the study: the median number of bleeds in the previous 12 months was 15.0 in the 2x/week "failed" group compared to 4.5 and 3.0 in the every 5-day, or every 7-day groups, respectively.

An overview of these data is shown in Table 4.

Table 4. Disease characteristics –Main and Interim Extension study (Part A, ITT population)

	Main study		Interim Extension	
	On-demand group (N=20)	Prophylaxis (N=112)	On-demand group (N=14)	Prophylaxis (N=107)
Number of bleeds in previous 12 months				
Mean ± SD	27.9 ± 17.8	13.2 ± 18.0	30.1 ± 19.0	13.4 ±18.1
Median (range)	22.0 (6 to 64)	7.0 (0 to 98)	25.5 (6 to 64)	8.0 (0 to 98)
Number of joint bleeds in previous 12 months				
Mean ± SD	23.6 ± 18.8	9.5 ± 15.2	26.1 ± 20.5	9.7 ± 15.4
Median (range)	18.5 (5 to 62)	5.0 (0 to 98)	19.5 (5 to 62)	5.0 (0 to 98)
Target joint for bleeds?				
No	4 (20.0%)	31 (27.7%)	3 (21.4%)	30 (28.0%)
Yes	16 (80.0%)	81 (72.3%)	11 (78.6%)	77 (72.0%)
Number of target joints per patient				
Mean ± SD	2.5 ± 2.1	1.5 ± 1.5	2.7 ± 2.3	1.5 ± 1.4
Median (range)	2.0 (0 to 8)	1.0 (0 to 6)	2.5 (0 to 8)	1.0 (0 to 6)
Number of target joints				
0	4 (20.0%)	31 (27.7%)	3 (21.4%)	30 (28.0%)
1	3 (15.0%)	33 (29.5%)	2 (14.3%)	32 (29.9%)
2	4 (20.0%)	23 (20.5%)	2 (14.3%)	23 (21.5%)
3	4 (20.0%)	13 (11.6%)	2 (14.3%)	12 (11.2%)
4	2 (10.0%)	8 (7.1%)	2 (14.3%)	8 (7.5%)
5	2 (10.0%)	1 (0.9%)	2 (14.3%)	0 (0%)
6	0 (0%)	3 (2.7%)	0 (0%)	2 (1.9%)
7	0 (0%)	0 (0%)	0 (0%)	0 (0%)
8	1 (5.0%)	0 (0%)	1 (7.1%)	0 (0%)
Patient history of FVIII inhibitor				
No	19 (95.0%)	111 (99.1%)	13 (92.9%)	107 (100.0%)
Yes	1 (5.0%)	0 (0%)	1 (7.1%)	0 (0%)
Unknown	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Family history of FVIII inhibitor				
No	14 (70.0%)	101 (90.2%)	9 (64.3%)	96 (89.7%)
Yes	2 (10.0%)	2 (1.8%)	1 (7.1%)	3 2.8%)
Unknown	4 (20.0%)	9 (8.0%)	4 (28.6%)	8 (7.5%)
Type of FVIII gene mutation from history				
n	8 (100.0%)	55 (100.0%)	6 (100.0%)	52 (100.0%)
Intron 22 inversion	1 (12.5%)	21 (38.2%)	0 (0%)	21 (40.4%)
Missense mutation	1 (12.5%)	6 (10.9%)	1 (16.7%)	6 (11.5%)
Nonsense mutation	2 (25.0%)	1 (1.8%)	2 (33.3%)	1 (1.9%)
Small deletion	0 (0%)	3 (5.5%)	0 (0%)	3 (5.8%)
Splice site mutation	1 (12.5%)	1 (1.8%)	1 (16.7%)	1 (1.9%)
No mutation	0 (0%)	4 (7.3%)	0 (0%)	4 (7.7%)
Intron 1 inversion	1 (12.5%)	2 (3.6%)	0 (0%)	2 (3.8%)
Other	2 (25.0%)	17 (30.9%)	2 (33.3%)	14 (26.9%)

Source: Original from BLA 125661/0; Module 2.7.3 Summary of Clinical Efficacy, Table 3-9

Part B
Severe hemophilia A was confirmed for all subjects at screening. A familial history of hemophilia was documented for 9 of the 17 (52.9%) subjects and 1 (5.9%) subject had a familial history of an inhibitor to FVIII. One subject had a reported history of having a FVIII inhibitor.

Prior FVIII treatment type was on-demand for 6 of the 17 subjects (35.3%) and prophylaxis for 11 subjects (64.7%). HIV infection was recorded in 5 subjects (29.4%), and chronic hepatitis C, hepatitis C or hepatitis C antibody positive in 10 (58.8%), 5 (29.4%), or 1 subjects (5.9%), respectively.

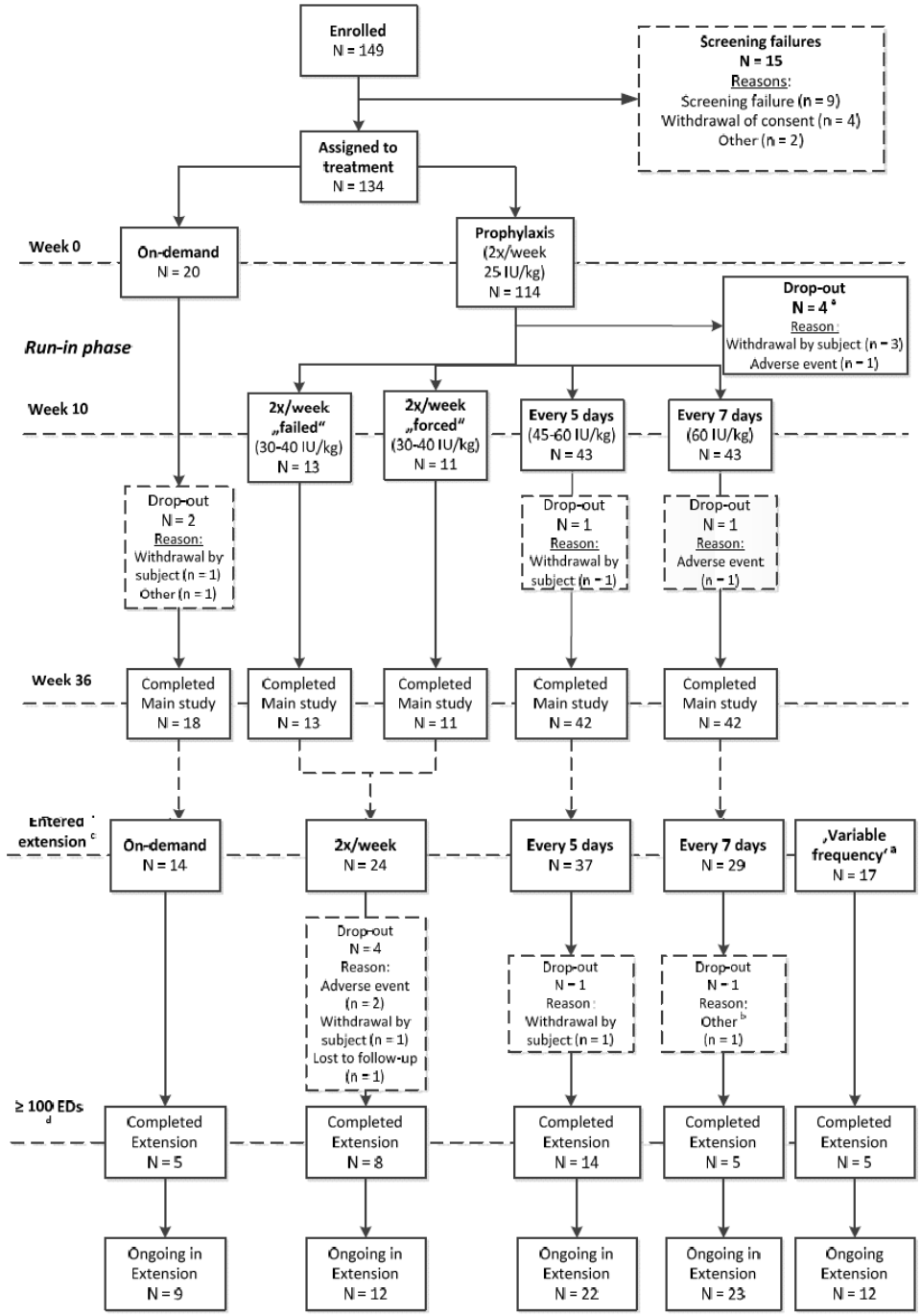
6.1.10.1.3 Subject Disposition
Figure 2 gives an overview on the subject disposition for Part A of the main and interim extension study. Overall, 149 subjects were enrolled and 134 subjects completed screening and were eligible for treatment in Part A. Twenty subjects selected the on-demand treatment arm and 114 subjects received prophylaxis. A total of 126 subjects (on-demand: 18 subjects; prophylaxis: 108 subjects) completed the main study (see Figure 2 for reasons of discontinuation).

Of the 121 subjects who entered the extension (data cut-off: January 9, 2015), 5 of 14 subjects in the on-demand group and 32 of 107 subjects in the prophylaxis group completed the study. Six subjects (all from the prophylaxis group) discontinued treatment before the cut-off date for this interim analysis: two withdrew consent, two due to AEs, one was lost to follow-up, and one discontinued for ‘other’ reasons involving nonadherence to the study protocol. As of the cut-off date for this interim analysis, 9 subjects in the on-demand group and 69 subjects in the prophylaxis group were on-going in the extension.

Preliminary data for Ongoing Extension (Data Cut-off: February 15, 2017)

A total of 70 (57.9%) subjects completed treatment in the extension. Twelve subjects (all from the prophylaxis groups) had discontinued the extension, main reasons were withdrawal by the subject (three subjects) and AEs (two subjects), six “other” reasons (five of six subjects left the study after completing the extension in Japan [not in global extension], one lost to follow-up). Thirty-nine (32.2%) subjects were still on-going in the extension.

Figure 2. Part A Subject disposition (main study and extension)

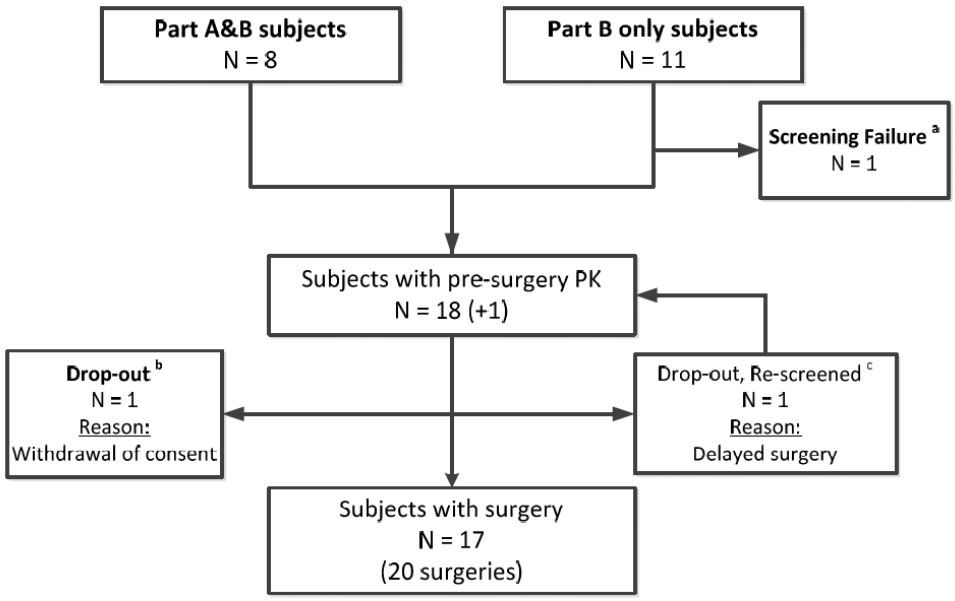


a 'Variable frequency' indicates patients who changed the treatment regimen at least once during extension.
b Other = withdrawn by sponsor decision because of a trip to Mexico
c Prophylaxis patients entering the extension could continue their prophylaxis regimen as it was at the completion of the main trial, or had the option to switch to one of the other prophylaxis regimens. On-demand patients entering the extension could continue their on-demand treatment or had the option to switch to one of the prophylaxis regimens. Any patient on a prophylaxis regimen during the extension could switch to one of the other prophylaxis regimens at any time.
d Patients were considered to be completers if they accumulated at least 100 EDs and completed end of extension study procedures.
e Two patients discontinued after a single dose of study drug and were excluded from the ITT population because no efficacy data for these patients were available. Two patients dropped-out during the run-in phase prior to week 10 and were therefore excluded from the main efficacy assessment from week 10 to 36.

Source: BLA 125661/0; Module 2.7.3 Summary of Clinical Efficacy, Figure 3-1

Figure 3 gives an overview on the subject disposition for Part B of the main and extension study. A total of 19 subjects had signed informed consent for major surgery during Part B and the extension of the study. One subject was a screening failure. Another subject entered Part B, performed pre-surgery PK, became a drop-out, and was re-screened successfully at a later stage. A third subject withdrew consent after the PK assessment but before major surgery was performed. Therefore, 17 subjects had a total of 20 major surgeries.

Figure 3. Part B Subject disposition (main study and extension)



a Subject (b) (6)
b Subject (b) (6)
c Subject (b) (6) dropped out due to delayed surgery
Source: BLA 125661/0; Module 2.7.3 Summary of Clinical Efficacy, Figure 3-4

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

Part A

In Table 5, the ABR is presented for the different prophylaxis regimens and the on-demand group for the main study. 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. During the 36-week treatment period, the median ABR was 2.82 when all prophylaxis groups were combined and 24.13 for the subjects in the on-demand group.

Table 5. ABR in Main study (ITT population)

	On-demand	Prophylaxis groups					
	Week 0 to 36	Week 0 to 10	After Week 10 to 36 [a]				
		Total	2x/week failed [b]	2x/week forced [b]	Every 5 days	Every 7 days	Total prophylaxis [c]
N	20	112	13	11	43	43	110 [d]
Mean ± SD	28.83 ± 17.84	4.10 ± 6.79	7.24 ±7.50	2.21 ± 2.72	3.30 ± 4.26	6.43 ± 10.04	4.88 ± 7.49
Minimum	8.7	0.0	0.0	0.0	0.0	0.0	0.0
Q1	17.84	0.0	2.01	0.00	0.0	0.0	0.0
Median	***24.13***	***0.0***	***4.11***	***1.93***	***1.93***	***3.85***	***2.09***
Q3	37.25	5.0	10.56	5.24	4.23	6.47	6.05
Maximum	83.2	30.0	26.1	7.7	16.1	53.1	53.1
Proportion of patients who had bleeds							
No	0 (0%)	65 (58.0%)	2 (15.4%)	5 (45.5%)	19 (44.2%)	16 (37.2%)	42 (38.2%)
Yes	20 (100%)	47 (42.0%)	11 (84.6%)	6 (54.5%)	24 (55.8%)	27 (62.8%)	68 (61.8%)

Note: The ABR refers to 'total bleeds' = number of spontaneous bleeds + number of trauma bleeds.

a Excluding rescue bleeds. A "rescue bleed" was a bleed that occurred after the regimen was increased. The period after regimen change was excluded.

b '2x/week, failed' denotes patients with ≥ 2 spontaneous bleeds in Weeks 0-10 who stayed on 2x/week regimen after Week 10 according to the protocol. '2x/week, forced' denotes patients with < 2 spontaneous bleeds in Weeks 0 to 10 who were forced due to treatment arm caps to stay on 2x/week regimen after Week 10.

c 'Total prophylaxis' combines all prophylaxis regimens.

d Two patients dropped out prior to Week 10.

Source: BLA 125661/0.23; Response to FDA's Information Request #18, Table 3-15 on page 6

The responder rate was evaluated in subjects who were enrolled in the prophylactic treatment arm for an evaluation period starting from Week 10 to Week 36. Table 6 shows the point-estimated responder rates (less than 9 bleeds/year) in the main study; a minimum response rate of >50% for each corresponding treatment arm was achieved.

Table 6. Responder rates (less than 9 bleeds/year) by prophylaxis group in Main study, Weeks 10-36 (ITT population)

	2x/week, failed (N=13)	2x/week, forced (N=11)	Every 5 days (N=43)	Every 7 days (N=43)	Total (N=110)
N	13 (100.0%)	11 (100.0%)	43 (100.0%)	43 (100.0%)	110 (100%)
No	4 (30.8%)	0	7 (16.3%)	14 (32.6%)	25 (22.7%)
Yes	9 (69.2%)	11 (100.0%)	36 (83.7%)	29 (67.4%)	85 (77.3%)

Abbreviations: N = number of subjects

Source: BLA 125661/0; Module 5.3.5.2 Amended CSR PH-37583, Table 9-6

Sensitivity analyses were performed for responders defined as prophylaxis subjects with less than 3, 5, 7, or 11 bleeds per year who did not increase their dosing frequency. At each level greater than 3 (5, 7, 9, or 11), a responder rate of ≥ 50% was achieved. The responder rate of 50% was also achieved for the 2x/week "forced" and every 5-day treatment groups using a threshold of 3 ABR.

Reviewer Comment: The responder rates presented in the submission were all point estimates. Due to the small sample size, using lower confidence limit (LCL) would give more reliable estimate. The 95% LCLs of responder rate (using, 3, 5, 7, 9, or 11 as threshold) for 2x/week failed group were all lower than 50%. The 95% LCLs of responder rate for all the prophylaxis groups were lower than 50% using a threshold of 3 ABR.

Extension

As shown in Table 7, for the 107 subjects entering the extension study, the median ABR in the combined prophylaxis regimens 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 subjects with "variable frequency" groups. The proportion of subjects who had no bleeds during the extension ranged from 5.9% in the "variable frequency" group to 48.3% in the every 7-day group. For subjects in the on-demand group, the median ABR was 32.96.

Table 7. ABR in Interim Extension study (ITT population)

		Prophylaxis groups				
	On-demand (N = 14)	2x/week (N = 24)	Every 5 days (N = 37)	Every 7 days (N = 29)	Variable frequency [a] (N = 17)	Total prophylaxis (N = 107) [b]
Mean ± SD	32.41 ± 17.53	3.95 ± 4.93	4.41 ± 6.79	1.56 ±3.72	5.83 ± 7.05	3.76 ± 5.85
Minimum	13.4	0.0	0.0	0.0	0.0	0.0
Q1	22.55	0.39	0.00	0.00	1.19	0.00
Median	***32.96***	***2.21***	***1.17***	***0.54***	***3.94***	***1.17***
Q3	35.64	4.32	5.59	1.04	6.36	4.33
Maximum	82.8	16.2	34.9	16.2	22.8	34.9
Proportion of patients who had bleeds						
No	0 (0%)	6 (25.0%)	12 (32.4%)	14 (48.3%)	1 (5.9%)	33 (30.8%)
Yes	14 (100%)	18 (75.0%)	25 (67.6%)	15 (51.7%)	16 (94.1%)	74 (69.2%)

a 'Variable frequency' indicates patients who changed the treatment regimen at least once during extension.
b 'Total prophylaxis' combines all prophylaxis regimens.

Source: BLA 125661/0; Module 2.7.3 Summary of Clinical Efficacy, Table 3-19

Preliminary data for Ongoing Extension (Data Cut-off: February 15, 2017)

One hundred and seven subjects receiving prophylaxis treatment during the extension had 705 total bleeds over the reporting period for this interim analysis. The median ABR in any prophylaxis regimen was 1.53. The median ABR by regimens were 1.89 for 2x/week, 1.34 for every 5-day, 0.69 for every 7-day and 3.73 for the 'variable frequency' groups. Fourteen subjects receiving on-demand treatment during the extension had 1,039 total bleeds. The median ABR was 33.47.

Part B

Table 8 summarizes major surgeries performed in Part B of the main and interim extension study. A total of 17 subjects successfully completed 20 surgeries in Part B of the main (14 subjects with 17 surgeries) or extension study (3 subjects with 3 surgeries) using BAY 94-9027 for hemostasis. Fourteen major surgeries were orthopedic joint surgeries (three arthroplasties, six joint replacements and three synovectomies, two other joint procedures). Treatment with BAY 94-9027 provided "good" or "excellent" hemostatic control during all major surgeries. The initial BAY 94-9027 pre-surgery doses administered ranged between 2,500 and 5,000 IU. The median total dose per surgery was 16,250 IU with a median of 35.1 IU/kg/infusion and 218.8 IU/kg per surgery. Blood loss was within expected levels, and four subjects received blood transfusions. Hemostatic control was assessed at the post-surgical visit as "good" or "excellent" in 17 out of 20 cases (85%). In three cases post-operative hemostasis was assessed as moderate.

Table 8. Listing of major surgeries in the Main and Interim Extension study (Part B, ITT population)

Subject number Age / Race	Type of surgery / Reported name of procedure	Total dose on surgery day [IU]	Surgery duration [min]	Blood loss [mL] (during and post-surgery)	Physician assessment of adequacy of hemostasis (during / post-surgery)	Blood transfusion needed?
Patients with major surgeries during PROTECT VIII Main study						
(b) (6) 42-year old / White	Elective / Left shoulder arthroscopy and subacromial decompression	5000	90	0/0	Good/Good	No
(b) (6) 45-year old / White	Elective / Open repair of recurrent L inguinal and umbilical hernias	6000	115	50/0	Excellent/Excellent	No
(b) (6) 51-year old / White	Elective / Right total hip arthroplasty	8000	169	250/0	Excellent/Excellent	No
(b) (6) 51-year old / White	Elective / Placement of infrapubic 3-piece inflatable penile prosthesis	5000	139	50/0	Good/Excellent	No
(b) (6) 61-year old / Not reported	Elective / Removal of right knee prosthesis	4000	196	590/930	Excellent/Good	No
	Elective / Re-implantation of right knee prosthesis	3000	231	1000/1430	Good/Excellent	Yes
(b) (6) 37-year old / White	Elective / Replacement left knee	5000	150	0/1100	Good/Moderate	Yes
(b) (6) 41-year old / White	Elective / Right knee arthroplasty re-implantation	6500	160	400/2950	Good/Good	Yes
(b) (6) 32-year old / White	Elective / Right ankle arthroplasty	7500	130	500/0	Good/Good	No
(b) (6) 57-year old / White	Elective / Total knee replacement (right)	5000	183	0/70	Good/Good	No
(b) (6) 24-year old / White	Elective / Surgical tooth extraction (impacted) and simple tooth extraction	4000	35	10/0	Excellent/Excellent	No
(b) (6) 25-year old / White	Elective / Synovectomy and judet plus soft tissue release left knee/thigh	7500	144	1000/1350	Good/-	Yes
	Emergency / Evacuation of hematoma left knee/thigh	6000	143	600/255	Good/Moderate	Yes
(b) (6) 33-year old / Asian	Elective / Arthroscopic synovectomy	7000	190	30/0	Good/Moderate	No
(b) (6) 13-year old / White	Elective / Synovectomy - right knee	2500	30	30/200	Excellent/Excellent	No
(b) (6) 26-year old / White	Elective / Surgical extractions teeth 26 and 36, alveoloplasty post extraction	4770	76	10/0	Excellent/Excellent	
	Elective / Surgical extractions teeth 17,12 and 46, alveoloplasty post extraction	5000	40	7/0	Excellent/Excellent	No
Patients with major surgeries during PROTECT VIII Interim Extension study						
(b) (6) 28-year old / White	Elective / Arthroscopic left subtalar fusion	4000	164	5/0	Good/Good	No
(b) (6) 37-year old / White	Elective / Left total knee replacement	8000	100	300/190	Good/Good	No
(b) (6) 30-year old / White	Elective / Total right ankle replacement	10,000	217	150/0	Good/Good	No

Note: Surgery duration includes both surgery and related anesthesia.
Source: BLA 125661/0; Module 2.7.3 Summary of Clinical Efficacy, Table 3-63

6.1.11.2 Analyses of Secondary Endpoints

Response to treatment of bleeds

Table 9 (main study) and Table 10 (interim extension) display a summary of the subjects' assessment of adequacy of hemostasis. Response to treatment of bleeds was rated as either good or excellent for 65.9% of subjects in on-demand group and 82.6% of subjects in prophylaxis group. A slight increase in the proportion of subjects with a rating of good or excellent was noticed during the reporting period of the extension study (on demand group: 70.4%; prophylaxis group: 86.5%). No obvious differences in adequacy of hemostasis were noted between the different prophylaxis arms in both the main and extension studies. For the majority of subjects in all prophylaxis groups, the treatment response was rated as either good or excellent (2x/week: 72.1%, every 5 days: 86.7%, every 7 days: 89.7%).

Table 9. Patient assessment of response to treatment of bleeds in the Main study (ITT population)

	On-demand (N = 20)	Prophylaxis (N = 112)	Total (N = 132)
Number of bleeds	388	317	705
missing assessment	4	7	11
Number of bleeds with assessment [a]	384 (100.0%)	310 (100.0%)	694 (100.0%)
Excellent or good	***253 (65.9%)***	***256 (82.6%)***	***509 (73.3%)***
Moderate	115 (29.9%)	47 (15.2%)	162 (23.3%)
Poor	16 (4.2%)	7 (2.3%)	23 (3.3%)

N = number of patients
a Referring to total bleeds, ie, sum of spontaneous and trauma bleeds with assessment available.
Source: BLA 125661/0.23; Response to FDA's Information Request #18, Table 3-56 on page 9

Table 10. Patient assessment of response to treatment of bleeds in the Interim Extension study (ITT population)

	On-demand (N = 14)	Prophylaxis (N = 107)	Total (N = 121)
Number of bleeds	514	428	942
missing assessment	0	5	5
Number of bleeds with assessment [a]	514 (100.0%)	423 (100.0%)	937 (100.0%)
Excellent or good	***362 (70.4%)***	***366 (86.5%)***	***728 (77.7%)***
Moderate	137 (26.7%)	53 (12.5%)	190 (20.3%)
Poor	15 (2.9%)	4 (0.9%)	19 (2.0%)

N = number of patients
a Referring to total bleeds, ie, sum of spontaneous and trauma bleeds.
Source: BLA 125661/0; Module 2.7.3 Summary of Clinical Efficacy, Table 3-57

Summary of treatment attributes

The number of infusions used to treat a bleed is summarized in Table 11 for the main study and in Table 12 for the interim extension study. In both study parts approximately 90% of the bleeds were treated with one or two infusions. There was no noticeable difference between the on-demand and prophylaxis groups. Percentages of bleeds were treated with 1 infusion in the main and interim extension study were 81.1% and 83.0%, respectively. The median time interval to the first follow-up infusion was approximately one day in both the main and extension parts of the study.

Table 11. Summary of treatment attributes for bleeds, Weeks 0 to 36 in the Main study (ITT population)

	On-demand (N=20)	Prophylaxis (N=112)	Total (N=132)
Number of infusions to control a bleed [a]			
number of bleeds	388	317	705
Mean	1.4	1.5	1.5
SD	1.1	1.3	1.2
Min	1	1	1
Q1	1.0	1.0	1.0
Median	***1.0***	***1.0***	***1.0***
Q3	1.0	1.0	1.0
Max	9	9	9
Number of bleeds per treatment frequency category			
number of bleeds	388 (100.0%)	317 (100.0%)	705 (100.0%)
1 infusion	309 (79.6%)	263 (83.0%)	572 (81.1%)
1 or 2 infusions	***354 (91.2%)***	***285 (89.9%)***	***639 (90.6%)***
≥ 3 infusions	34 (8.8%)	32 (10.1%)	66 (9.4%)
Time to first follow-up infusion [days]			
number of bleeds	79	54	133
Mean	2.81	1.08	2.11
SD	12.60	0.57	9.73
Min	0.2	0.4	0.2
Q1	0.66	0.72	0.69
Median	***1.01***	***0.98***	***1.00***
Q3	1.31	1.18	1.23
Max	111.5	3.0	111.5

a Referring to total bleeds, i.e., sum of spontaneous and trauma bleeds.

Source: BLA 125661/23; Response to FDA's Information Request #18, Table 3-53 on page 9

Table 12. Summary of treatment attributes for bleeds in the Interim Extension study (ITT population)

	On-demand (N = 14)	Prophylaxis (N = 107)	Total (N = 121)
Number of infusions to control a bleed [a]			
number of bleeds	514	428	942
Mean	1.3	1.5	1.4
SD	0.8	2.1	1.5
Min	1	1	1
Q1	1.0	1.0	1.0
Median	***1.0***	***1.0***	***1.0***
Q3	1.0	1.0	1.0
Max	7	35	35
Number of bleeds per treatment frequency category			
number of bleeds	514 (100.0%)	428 (100.0%)	942 (100.0%)
1 infusion	424 (82.5%)	358 (83.6%)	782 (83.0%)
1 or 2 infusions	***475 (92.4%)***	***394 (92.1%)***	***869 (92.3%)***
≥ 3 infusions	39 (7.6%)	34 (7.9%)	73 (7.7%)
Time to first follow-up infusion [days]			
number of bleeds	90	70	160
Mean	1.30	1.15	1.23
SD	0.59	0.74	0.66
Min	0.4	0.4	0.4
Q1	0.97	0.73	0.90
Median	***1.06***	***0.98***	***1.01***
Q3	1.40	1.24	1.37
Max	3.5	4.8	4.8

a Referring to total bleeds, ie, sum of spontaneous and trauma bleeds.

Source: BLA 125661/0; Module 2.7.3 Summary of Clinical Efficacy, Table 3-54

Summary of bleeds by type

The mean ABR of spontaneous bleeds was 17.19 ± 13.19 bleeds/year (median: 14.29 bleeds) in the on-demand group and 3.41 ± 6.72 bleeds/year (median: 0 bleeds) in the prophylaxis groups combined. Most of bleeds were joint bleeds (78.4% in the on-

demand group and 74.4% in the prophylaxis groups combined) and 63.8% of those bleeds were in target joints for the on-demand group and 45.1% in the prophylaxis groups combined. Table 13 summarizes the calculated ABRs by type of bleed in the individual prophylaxis regimen during the main study. For spontaneous and trauma bleeds the median ABR was 0 for all prophylaxis regimens except for spontaneous bleeds during the every 7-day regimen with an ABR of 1.93. For joint bleeds the median ABR was approximately 2 for all regimens during the following 26 weeks of treatment.

Table 13. Summary of bleeds in prophylaxis regimens by type in the Main study (ITT population)

	Week 0-10	Week 10 – 36 [a]			
	Total [b] (N = 112)	2x/week (N = 24)	Every 5 days (N = 43)	Every 7 days (N = 43)	Total prophylaxis [c] (N= 110)
Annualized number of spontaneous bleeds					
Mean ± SD	2.81 ± 5.64	2.62 ± 3.69	1.84 ± 2.61	5.42 ± 9.79	3.41 ± 6.72
Minimum	0.0	0.0	0.0	0.0	0.0
Q1	0.00	0.00	0.00	0.00	0.00
Median	***0.00***	***0.00***	***0.00***	***1.93***	***0.00***
Q3	4.81	4.06	3.99	6.33	4.17
Maximum	26.1	12.0	8.2	53.1	53.1
Annualized number of trauma bleeds					
Mean ± SD	1.29 ± 2.81	2.32±3.79	1.47±3.16	1.00±2.59	1.47±3.12
Minimum	0.0	0.0	0.0	0.0	0.0
Q1	0.00	0.00	0.00	0.00	0.00
Median	***0.00***	***0.00***	***0.00***	***0.00***	***0.00***
Q3	0.00	3.05	2.09	0.00	1.98
Maximum	15.6	14.1	14.0	14.4	14.4
Annualized number of joint bleeds					
Mean ± SD	3.13 ± 5.94	3.85 ± 4.17	2.51 ± 3.45	4.65 ± 9.14	3.64 ± 6.43
Minimum	0.0	0.0	0.0	0.0	0.0
Q1	0.00	0.00	0.00	0.00	0.00
Median	***0.00***	***2.05***	***1.86***	***1.92***	***1.93***
Q3	4.86	6.02	3.99	6.26	5.24
Maximum	30.0	15.5	14.0	53.1	53.1

a Excluding rescue bleeds. A "rescue bleed" was a bleed that occurred after the regimen was increased. The period after regimen change was excluded.
b Two patients dropped out prior to Week 10.
c 'Total prophylaxis' refers to all prophylaxis regimens combined, ie, the sum of 2x/week, every 5 days, and every 7 days.

Source: BLA 125661/0.23; Response to FDA's Information Request #18, Table 3-45 on page 8

During the extension phase of the study, the mean ABR of spontaneous bleeds was 21.26 ± 12.81 bleeds/year (median: 18.04 bleeds) in the on-demand group and 2.37 ± 3.99 bleeds/year (median: 0.62 bleeds) in the prophylaxis groups combined. Most of bleeds were joint bleeds (72.2% in on-demand group and 73.1% in prophylaxis groups combined) and 66.6% of those bleeds were in target joints for the on-demand group and 36.4% in the prophylaxis groups combined. The highest median ABR occurred in the group of subjects with "variable frequency", indicating that the originally assigned dose regimen was not suitable for the subject and that higher frequencies were required for a good prevention of bleeding events. For joint bleeds, a decrease was noticed during the extension phase for all prophylaxis regimens in comparison to the main study: median ABRs were 0.85, 1.11, and 0 for the 2x/week, every 5-day, and every 7-day regimens (Table 14).

Table 14. Summary of bleeds in prophylaxis arms by type in the Interim Extension study (ITT population)

	2x/week (N=24)	Every 5 days (N=37)	Every 7 days (N=29)	Variable frequency (N=17) [a]	Total prophylaxis (N=107) [b]
Annualized number of spontaneous bleeds					
Mean ± SD	1.97 ± 2.65	2.77 ±3.82	1.20 ±3.61	4.08 ± 5.79	2.37 ± 3.99
Minimum	0.0	0.0	0.0	0.0	0.0
Q1	0.00	0.00	0.00	0.73	0.00
Median	***1.09***	***0.71***	***0.00***	***2.27***	***0.62***
Q3	2.93	4.02	0.62	4.11	3.17
Maximum	10.0	14.7	15.2	22.8	22.8
Annualized number of trauma bleeds					
Mean ± SD	1.98 ± 3.27	1.65 ± 3.88	0.36 ± 0.74	1.75 ±3.53	1.39 ± 3.14
Minimum	0.0	0.0	0.0	0.0	0.0
Q1	0.00	0.00	0.00	0.00	0.00
Median	***0.00***	***0.00***	***0.00***	***0.67***	***0.00***
Q3	3.07	1.11	0.52	1.27	1.11
Maximum	12.4	20.2	3.0	14.0	20.2
Annualized number of joint bleeds					
Mean ± SD	1.99 ± 3.17	3.31 ± 4.56	1.08 ± 2.55	4.84 ± 6.49	2.65 ± 4.36
Minimum	0.0	0.0	0.0	0.0	0.0
Q1	0.00	0.00	0.00	0.78	0.00
Median	***0.85***	***1.11***	***0.00***	***3.25***	***0.80***
Q3	2.32	4.44	0.88	4.79	3.37
Maximum	12.4	18.6	13.0	22.8	22.8

a 'Variable frequency' indicates patients who changed the treatment regimen at least once during extension.
b 'Total prophylaxis' refers to all prophylaxis regimens combined.

Source: BLA 125661/0; Module 2.7.3 Summary of Clinical Efficacy, Table 3-46

Summary of bleeds by location and severity

In Table 15 and Table 16, bleed locations and severity of bleeds are presented by the individual prophylaxis regimen for the main and interim extension study, respectively. Irrespective of the treatment regimen, most of the bleeds were joint bleeds. The majority of bleeds were either mild or moderate in severity across all regimens. The number of severe bleeds was low and occurred with similar frequency in all regimens.

Table 15. Summary of bleeds in prophylaxis arms by location and severity, Weeks 10 to 36, excluding rescue bleeds in the Main study (ITT population)

	2x/week [a] (N = 24)	Every 5 days (N = 43)	Every 7 days (N = 43)	Total prophylaxis [b] (N = 110)
Bleed location				
n	60 (100%)	70 (100%)	76 (100%)	206 (100%)
Missing	0 (0%)	0	0	0
Joint	47 (78.3%)	53 (75.7%)	52 (68.4%)	152 (73.8%)
Muscle	14 (23.3%)	7 (10.0%)	12 (15.8%)	33 (16.0%)
Skin/Mucosa	1 (1.7%)	4 (5.7%)	3 (3.9%)	8 (3.9%)
Internal	0	4 (5.7%)	2 (2.6%)	6 (2.9%)
Other	1 (1.7%)	4 (5.7%)	8 (10.5%)	13 (6.3%)
Bleed severity				
n	60 (100.0%)	70 (100%)	76 (100%)	206 (100%)
Missing	0	0	1 (1.3%)	1 (0.5%)
Mild	31 (51.7%)	36 (51.4%)	32 (42.1%)	99 (48.1%)
Moderate	26 (43.3%)	31 (44.3%)	39 (51.3%)	96 (46.6%)
Severe	3 (5.0%)	3 (4.3%)	4 (5.3%)	10 (4.9%)

A "rescue bleed" was a bleed that occurred after the regimen was increased. The period after regimen change was excluded.
N = number of patients; n = number of bleeds
a For 2x/week, '2x/week failed' and '2x/week forced' dosing were combined. '2x/week failed' denotes patients with ≥ 2 spontaneous bleeds in Weeks 0-10 who stayed on 2x/week regimen after Week 10 according to the protocol. '2x/week forced' denotes patients with < 2 spontaneous bleeds in Weeks 0-10 who were forced due to randomization arm caps to stay on 2x/week regimen after Week 10.
b 'Total prophylaxis' refers to all prophylaxis regimens combined.

Source: BLA 125661/0; Module 2.7.3 Summary of Clinical Efficacy, Table 3-49

Table 16. Summary of bleeds in prophylaxis arms by location and severity in the Interim Extension study (ITT population)

	2x/week (N=24)	Every 5 days (N=37)	Every 7 days (N=29)	Variable frequency [a] (N=17)	Total prophylaxis [b] (N=107)
Bleed location					
n	93 (100.0%)	192 (100.0%)	38 (100.0%)	105 (100.0%)	428 (100.0%)
Missing	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)
Joint	58 (62.4%)	140 (72.9%)	24 (63.2%)	91 (86.7%)	313 (73.1%)
Muscle	25 (26.9%)	22 (11.5%)	8 (21.1%)	9 (8.6%)	64 (15.0%)
Skin/Mucosa	1 (1.1%)	25 (13.0%)	1 (2.6%)	6 (5.7%)	33 (7.7%)
Internal	0 (0%)	6 (3.1%)	0 (0%)	0 (0%)	6 (1.4%)
Other	9 (9.7%)	6 (3.1%)	5 (13.2%)	2 (1.9%)	22 (5.1%)
Bleed severity					
n	93 (100.0%)	192 (100.0%)	38 (100.0%)	105 (100.0%)	428 (100.0%)
Missing	5 (5.4%)	3 (1.6%)	0 (0%)	0 (0%)	8 (1.9%)
Mild	36 (38.7%)	74 (38.5%)	22 (57.9%)	56 (53.3%)	188 (43.9%)
Moderate	43 (46.2%)	94 (49.0%)	10 (26.3%)	43 (41.0%)	190 (44.4%)
Severe	9 (9.7%)	21 (10.9%)	6 (15.8%)	6 (5.7%)	42 (9.8%)

N = number of patients; n = number of bleeds
a 'Variable frequency' indicates patients who changed the treatment regimen at least once during extension.
b 'Total prophylaxis' refers to all prophylaxis regimens combined.

Source: BLA 125661/0; Module 2.7.3 Summary of Clinical Efficacy, Table 3-50

Hemostatic outcome of minor surgeries

A total of 34 minor surgeries performed in 19 subjects were reported during Part A of the main or interim extension study. More than half of these surgeries were dental extractions or other dental procedures. No subjects required blood transfusions. The adequacy of hemostasis during minor surgeries was assessed as either "good" or "excellent" in all cases where an assessment was reported.

6.1.11.3 Subpopulation Analyses

For the subgroups prospectively identified and listed in Section 6.1.9, median ABRs are presented for each prophylaxis regimen in Table 17. In summary, factors that seem to influence the outcome are the presence of target joints, age > 35 years and Asian population; all three factors may overlap as target joints are more frequent in older subjects and those who have not received prophylaxis as standard of care (Asian population).

Table 17. Median ABRs in prophylaxis arm by subgroups, Weeks 10-36, excluding rescue bleeds in the Main study (ITT population)

	2x/week (N=24)	Every 5 days (N=43)	Every 7 days (N=43)	Total (N=110)
Target Joints				
No	0.0 (n = 3)	0.0 (n = 15)	4.0 (n = 12)	1.0 (n = 30)
Yes	3.9 (n = 21)	2.0 (n = 28)	2.1 (n = 31)	2.1 (n = 80)
Age group 1				
< 18 years	0.0 (n = 3)	1.1 (n = 6)	18.4 (n = 3)	1.0 (n = 12)
≥ 18 years	4.0 (n = 21)	1.9 (n = 37)	3.0 (n = 40)	2.1 (n = 98)
Age Group 2				
< 18 years	0.0 (n = 3)	1.1 (n = 6)	18.4 (n = 3)	1.0 (n = 12)
18 to 34 years	4.6 (n = 12)	2.1 (n = 17)	0.0 (n = 17)	2.0 (n = 46)
≥ 35 years	4.0 (n = 9)	0.0 (n = 20)	4.9 (n = 23)	4.0 (n = 52)
Race				
White	3.0 (n = 16)	1.9 (n = 29)	3.0 (n = 28)	2.0 (n = 73)
Black or African American	(n = 0)	4.1 (n = 1)	0.0 (n = 3)	2.0 (n =4)
Asian	3.1 (n = 8)	4.0 (n = 11)	3.2 (n = 8)	4.0 (n = 27)
Not reported	(n = 0)	0.0 (n = 2)	9.3 (n = 4)	2.5 (n = 6)
Region				
North America	3.7 (n = 6)	2.0 (n = 6)	3.8 (n = 11)	2.1 (n = 23)
Europe	1.9 (n = 9)	2.1 (n = 17)	4.4 (n = 15)	2.2 (n = 41)
Israel	3.9 (n = 1)	0.0 (n = 8)	1.9 (n = 7)	1.0 (n = 16)
Asia	3.1 (n = 8)	4.0 (n = 11)	3.2 (n = 8)	4.0 (n = 27)
South America	(n = 0)	0.0 (n = 1)	6.8 (n = 2)	0.0 (n = 3)
BMI				
< 25 kg/m^2	3.9 (n = 17)	2.1 (n = 24)	2.1 (n = 23)	2.1 (n = 64)
25 to 29 kg/m^2	1.9 (n = 5)	0.0 (n = 11)	3.2 (n = 14)	1.9 (n = 30)
≥30 kg/m^2	2.7 (n = 2)	0.9 (n = 8)	4.0 (n = 6)	2.9 (n = 16)
Previous treatment				
On-demand	4.0 (n = 9)	2.0 (n = 8)	2.1 (n = 5)	2.1 (n = 22)
Prophylaxis	2.1 (n = 15)	1.9 (n = 35)	4.2 (n = 38)	2.1 (n = 88)

A "rescue bleed" was a bleed that occurred after the regimen was increased.
For 2x/week, '2x/week failed' and '2x/week forced' dosing were combined. '2x/week failed' denotes patients with ≥ 2 spontaneous bleeds in Weeks 0-10 who stayed on 2x/week regimen after Week 10 according to the protocol. '2x/week forced' denotes patients with < 2 spontaneous bleeds in Weeks 0-10 who were forced due to randomization arm caps to stay on 2x/week regimen after Week 10.

Source: BLA 125661/0; Module 2.7.3 Summary of Clinical Efficacy, Table 3-67

6.1.11.4 Dropouts and/or Discontinuations

In Part A, two subjects discontinued after a single dose of study drug (one withdrew consent; one due to hypersensitivity reaction) and were excluded from the ITT population because no efficacy data for these subjects were available. They were included in the Safety population.

At the completion of Part A of the main study, 126 subjects had completed treatment in Part A and 8 subjects had discontinued from the study. Of those subjects who discontinued, five withdrew consent, two were due to adverse events, and one was for "other" reasons involving non-adherence to the study protocol.

Of the 121 subjects who signed informed consent and received treatment during the Part A extension, 6 subjects (all from the prophylaxis groups) discontinued treatment before the cut-off date for the interim analysis. Of those subjects who discontinued,

two withdrew consent, two were due to adverse events, one was lost to follow-up, and one was for "other" reasons involving non-adherence to the study protocol.

A total of 19 subjects had signed informed consent for major surgery during Part B and the extension of the study. One subject entered Part B, performed pre-surgery PK, became a drop-out, and was re-screened successfully at a later stage. Another subject withdrew consent after the PK assessment but before major surgery was performed.

Preliminary data for Ongoing Extension (Cut-off: February 15, 2017)
A total of 70 (57.9%) subjects completed treatment in the extension. Twelve subjects (all from the prophylaxis groups) had discontinued the extension, main reasons were withdrawal by the subject (three subjects) and AEs (two subjects), six "other" reasons, (five of six subjects left the study after completing the extension in Japan [not in global extension], one lost to follow-up).

Reviewer Comment: Two subjects were excluded from the ITT population in Part A due to no efficacy data. I deem this reasonable. According to the protocol, the ITT population consisted of all safety subjects who had infusion/bleeding data in their EPD and CRF. So with no bleeding data recorded, there is no reason to believe these two subjects would have abnormally high or low ABRs. Other discontinuations throughout the study also appear reasonable and are unlikely to impact efficacy results.

6.1.11.5 Exploratory and Post Hoc Analyses
In a *post-hoc* analysis using a negative binomial regression model including an offset variable to account for different follow-up times, ABRs were compared between the on-demand group (Week 0 to 36) and the different prophylaxis regimens (Week 10 to 36) (see Table 18). The bleeding rate ratios from this model were 0.25 ($p = 0.0001$), 0.08 ($p < 0.0001$), 0.12 ($p < 0.0001$), and 0.17 ($p < 0.0001$), for the 2x/week "failed", 2x/week "forced", every 5-day, and every 7-day regimens, respectively in comparison to on-demand treatment. This indicated that the ABR was significantly reduced by 74.9% (2x/week "failed" regimen), 92.2% (2x/week "forced" regimen), 88.3% (every 5-day regimen), and 83.1% (every 7-day regimen) using any of the prophylaxis regimens in comparison to on-demand treatment.

Table 18. *Post-hoc* analysis-ABR comparison between the on-demand group and the prophylaxis regimens in the Main study (ITT population)

	On-demand Week 0 to 36 N = 20	Prophylaxis groups				
		By regimen: After Week 10 to 36 [a]				Total prophylaxis: Week 0 to 36
		2x/week failed N = 13	2x/week forced N = 11	Every 5 days N = 43	Every 7 days N = 43	N = 112
Mean ABR [b]	28.85	7.24	2.26	3.37	4.88	4.12
(95% CI)	(19.29, 43.15)	(4.13, 12.70)	(1.06, 4.81)	(2.36, 4.81)	(3.40, 7.02)	(3.35, 5.07)
Rate Ratio		0.25	0.08	0.12	0.17	0.14
(95% CI)		(0.13, 0.50)	(0.03, 0.18)	(0.07, 0.20)	(0.10, 0.29)	(0.09, 0.23)
% Reduction		74.9	92.2	88.3	83.1	85.7
(95% CI)		(49.9, 87.4)	(81.6, 96.7)	(80.0, 93.2)	(70.9, 90.2)	(77.0, 91.1)
p-value		0.0001	<0.0001	<0.0001	<0.0001	<0.0001

CI = confidence interval

Note: The ABR refers to 'total bleeds' = number of spontaneous bleeds + number of trauma bleeds.

a Excluding rescue bleeds. A "rescue bleed" was a bleed that occurred after the regimen was increased. The period after regimen change was excluded.

b The model estimated means can be different from the calculated means. Calculated means use all the actual data points to do the calculation, while estimated mean are retrieved from a regression model that fits the actual data points with a pre-specified statistical distribution. Usually a correctly selected statistical model should give more accurate estimate for the population than actual data points, which is just a sample from the population. And Negative Binomial model is such a model for bleed count data.

Rate ratios and percent reductions are prophylaxis versus on-demand. Nominal p-values are derived from negative binomial regression model including an offset variable to account for different follow-up times.

Source: BLA 125661/0.23; Response to FDA's Information Request #18, Table 3-16 on page 7

The negative binomial model was also used for a *post-hoc* analysis comparing ABRs in the every 5-day and every 7-day (completers) regimens, with the 2x/week "forced" regimen (Table 19). The bleeding rate ratios from this model were 1.50 (p = 0.40), and 1.19 (p =0.73) for every 5-day and every 7-day completers regimens, respectively in comparison to 2x/week "forced" regimen. This indicated that the ABR was increased in every 5-day and every 7-day completers regimens in comparison to 2x/week "forced" regimen, but the differences are not statistically significant.

Table 19. *Post-hoc* analysis-ABR comparison between "every 5 days", "every 7 days, completers" and "2X/week, forced" in the Main study (completers)

	2x/week forced n=11	Every 5 days n=43	2x/week forced n=11	Every 7 days n=32
Mean ABR	2.25	3.37	2.25	2.68
(95% CI)	(0.96, 5.26)	(2.24, 5.06)	(0.95, 5.34)	(1.63, 4.41)
Rate Ratio		1.50		1.19
(95% CI)		(0.58, 3.85)		(0.44, 3.24)
p-value		0.4012		0.7281

CI = confidence interval

Note: Nominal p-values are derived from negative binomial model including an offset variable to account for different follow-up times. Estimated bleeding rate and its CI for '2x/week, forced' arm can be slightly different when different terms are included in the model.

Source: BLA 125661/0; Module 2.7.3 Summary of Clinical Efficacy, Table 3-17

6.1.12 Safety Analyses

6.1.12.3 Deaths

No subjects died during the study (Part A, Part B, and Extension).

6.1.12.4 Nonfatal Serious Adverse Events

Part A

Four subjects in the on-demand treatment group experienced one SAE each during the study and one subject experienced three. None of the SAEs in the on-demand group were considered drug related by the investigator.

In the prophylaxis group, 10 subjects experienced 11 total SAEs. One (hypersensitivity to study drug) was considered to be study drug related and one study drug overdose was considered to be study drug related as required by the protocol.

With the exception of one case of blunt injury, all SAEs were reported to have resolved by the end of the observation period.

Extension

In the prophylaxis group, 20 subjects experienced 23 total SAEs. Three of these SAEs (abnormal liver function test and 2 events of back pain) considered to be study drug related. Two subjects experienced 3 AEs that were considered suspected unexpected serious adverse reactions (SUSARs) due to their unexpected occurrence (one subject on prophylaxis 2x/week experienced an event of elevated liver function tests of moderate intensity; one subject on prophylaxis 2x/week experienced Migratory back pain of severe intensity).

With the exception of one case of abnormal liver function test, all SAEs were reported to have been resolved or recovering/resolving by the end of the observation period. The subject with the unresolved abnormal liver function was withdrawn from the study due to the event, but later presented with active chronic hepatitis C and began treatment with ledipasvir and sofosbuvir.

Part B

There were two cases of low titer FVIII inhibitors (< 5 Bethesda Unit; preferred terms: anti-factor VIII antibody positive) which were reported as drug-related SAEs. One of them had a pre-existing low-titer FVIII inhibitor.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

I verified the primary and some second efficacy results for the pivotal PROTECT VIII study.

On-demand treatment and control of bleeding episodes

A total of 388 bleeding episodes in 20 subjects were treated with JIVI during Weeks 0 to 36 in the on-demand group and 317 bleeding episodes in 112 subjects in all prophylaxis groups. During the extension part of the study, 14 subjects receiving on-demand treatment and 107 subjects on routine prophylaxis, respectively, had 514 and 428 total bleeds over the reporting period for the interim analysis (data as of January 9, 2015). The majority of the bleeding episodes were localized in joints, and mild to moderate in severity. The majority of bleeds (approximately 90%) were successfully treated with 1 or 2 infusions in both the on-demand and prophylaxis group during both the main and extension parts of the study. The subjects' assessment of response to treatment was "good" or "excellent" in 65.9% of the on-demand and 82.6% of the prophylaxis groups during the main study. A slight increase in the proportion of

"good" or "excellent" treatment responses (on-demand: 70.4%; prophylaxis groups: 86.5%) was observed during the extension part of the study.

Perioperative management of bleeding
A total of 17 subjects completed 20 major surgeries in Part B of the main study (14 subjects with 17 surgeries) or extension study (3 subjects with 3 surgeries) using JIVI for hemostasis. Fourteen were orthopedic joint surgeries (3 arthroplasties, 6 joint replacements and 3 synovectomies, and 2 other joint procedures). Treatment with JIVI provided "good" or "excellent" hemostatic control during all major surgeries. The initial JIVI pre-surgery doses administered ranged between 2,500 and 5,000 IU. The median total dose per surgery was 218.8 IU/kg with a median of 35.1 IU/kg/infusion.

A total of 34 minor surgeries performed in 19 subjects were reported during the main or extension studies. More than half of these surgeries were dental extractions or other dental procedures. No subjects required blood transfusions. The adequacy of hemostasis during minor surgeries was assessed as either "good" or "excellent" in all reported cases. No hemostasis-related complications were reported.

Routine prophylaxis to reduce the frequency of bleeding episodes
One hundred and ten subjects received JIVI for routine prophylaxis during the main efficacy period (Weeks 10–36). Of these, 107 subjects participated in the optional extension study. All subjects in the prophylaxis treatment arms began treatment with twice weekly infusions of 25 IU/kg for 10 weeks (run-in phase). After the run-in phase, 88% of subjects (97 of 110) who experienced ≤1 breakthrough bleeds during first the 10 weeks of treatment qualified for randomization (1:1) to a less frequent dosing regimen of either every 5 days or every 7 days for an additional 26 weeks (Weeks 10–36). Subjects (N=43) assigned to the every 5-day treatment regimen began treatment with a dose of 45 IU/kg (up to 60 IU/kg). Forty-three subjects assigned to the every 7-day treatment arm were treated with a fixed dose of 60 IU/kg. Eleven subjects were in the "forced" group and 13 subjects were in the "failed" group. Both groups were on a regimen with twice weekly infusions of 30–40 IU/kg for the additional 26 weeks.

During the 26-week treatment period, the median ABR was 2.09 when all prophylaxis groups were combined, with similar ABR in all treatment regimens. Forty-two subjects (38.2%) in the prophylaxis arms had no bleeds during the 26-week period. For subjects in the on-demand group, median ABR was 24.13 during the 36-week treatment period.

In the main part of the study (Weeks 10–36), the majority (90%, 99/110) of subjects did not change their treatment regimens. All subjects (N=43; 100%) randomized to the every 5-day study arm and all subjects (N=11; 100%) in the "forced" 2 times per week arm completed the main study. The median ABR for total bleeds was 1.93 for subjects in the "forced" 2 times per week arm and 1.93 for subjects randomized to the every 5-day arm. Thirty-two of 43 (74%) subjects randomized to the every 7-days prophylaxis treatment arm, remained in assigned treatment arm and completed main study with a median ABR of 0.96.

During the extension of the study (cut-off: January 9, 2015), 84% (90/107) of all subjects did not change their treatment regimen. Seventy-four percent (79/107) of all subjects did not change their dose during the extension. The median ABR was 32.96 for subjects receiving on-demand treatment and 1.17 for all subjects on routine prophylaxis during the extension study. The median ABR for total bleeds in subjects on twice weekly (N=24 combined), every 5-day (N=37) and every 7-day (N=29) prophylaxis regimens in the extension study was 2.21, 1.17 and 0.54, respectively.

10.2 Conclusions and Recommendations

Based on the results of the PROTECT VIII study, adequate statistical evidence supports approval of the proposed indications of: on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis treatment to reduce the frequency of bleeding episodes in adults and adolescents (12 years of age and older) with hemophilia A.