Application Type	Original Application
STN	125566/0
CBER Received Date	November 25, 2014
PDUFA Goal Date	November 13, 2015
Division / Office	DHCR /OBRR
Priority Review	No
Reviewer Name(s)	L. Ross Pierce, MD
Review Completion Date / Stamped Date	November 9, 2015
Supervisory concurrence	
Applicant	Baxalta US Inc.
Established Name	Antihemophilic Factor (Recombinant), PEGylated
(Proposed) Trade Name	ADYNOVATE
Pharmacologic Class	Coagulation factor
Formulation(s), including Adjuvants, etc	Intravenous injection
Dosage Form(s) and Route(s) of Administration	Lyophilized Powder for Injectable Solution, Intravenous
Dosing Regimen	Calculated by body weight. Available in 250, 500, 1000, 2000 IU single use vials
Indication(s) and Intended Population(s)	Treatment and Control of bleeding episodes in adolescents and adults with hemophilia A. Routine prophylaxis to reduce the frequency of bleeding episodes in adolescents and adults with hemophilia A.

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Glossary

Abbreviation	Definition
ABR	annualized bleeding rate
AE	adverse event
ALT	alanine aminotransferase (SGPT)
ASAS	ADVATE safety analysis set
AST	aspartate aminotransferase (SGOT)
AUC	area under the curve
$AUC_{(0-\infty)}$	area under the plasma concentration curve from 0 to infinity
BAX 855	product code name for Baxter's PEGylated recombinant FVIII (rFVIII)
BU	Bethesda unit
CHO	Chinese hamster ovary
CI	confidence interval
CL	total body clearance
Cmax	maximum concentration in plasma
(e)CRF	(electronic) case report form
DMC	data monitoring committee
EC	ethics committee
ED	exposure day
ELISA	enzyme-linked immunoabsorbent assay
EMA	European Medicines Agency
EQ-5D	EuroQol-5 dimensions
FAS	full analysis set
FVIII	factor VIII
GCP	Good Clinical Practice
GEE	general estimating equation
GLM	general linear model
HAV	hepatitis A virus
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody

Abbreviation	Definition
HDL	high density lipoprotein
HIV	human immunodeficiency virus
h	hour(s)
HRQoL	health-related quality of life
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	international normalized ratio
IP	investigational product
IR	incremental recovery over time
IQR	Interquartile range, ie quartile 1 ; quartile 3 (Q1 ; Q3)
ITI	immune tolerance induction
ITT	Intent-to-treat analysis set
IU	international units
i.v.	intravenous(ly)
LDL	low density lipoprotein
LoQ	limit of quantification
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important differences
Min	minimum
MRT	mean residence time
NMC	non-medical complaint
OPE	observation period for efficacy
PCR	polymerase chain reaction
PCS	Physical Component Score
pdFVIII	plasma-derived factor VIII
PEG	polyethylene glycol
PK	pharmacokinetic(s)

Abbreviation	Definition
PKFAS	pharmacokinetic full analysis set
PPAS	per protocol analysis set
PRO	patient reported outcome
PTP	previously treated patient
Range	Minimum (Min) to Maximum (Max)
rFVIII	recombinant factor VIII
SAE	serious adverse event
SAER	serious adverse event report
SAS	safety analysis set
SD	standard deviation
SF-36	Short form-36 questionnaire
SIC	subject identification code
SWFI	sterile water for injection
$T_{1/2}$	half-life
Tmax	time to maximum concentration in plasma
US	United States
US CFR	US Code of Federal Regulations
VLDL	very low density lipoprotein
Vss	volume of distribution at steady state
VWF	von Willebrand factor
VWF Ag	von Willebrand factor antigen

Page numbers: All page numbers in this document refer to the electronic page number from the digital documents as numbered by Adobe Acrobat.

1. Executive Summary

ADYNOVATE or BAX 855 (Antihemophilic Factor (Recombinant), PEGylated; rFVIII, PEGylated) is a lyophilized protein manufactured in Chinese Hamster Ovary (CHO) cells. The fusion protein consists of a full length form of recombinant antihemophilic factor (b) (4) to the marketed Antihemophilic Factor (Recombinant) product, ADVATE) covalently conjugated to a polyethylene glycol (PEG) reagent. The product consists of a mixture of rFVIII molecules with varying degrees of PEGylation (varying ratios in the number of molecules of PEG moiety conjugated covalently to each rFVIII moiety) with the mean ratio being (b) (4) The PEG enables an increase of the plasma half-life through the reduction of the LRP-1 receptor-mediated clearance of the factor VIII molecule. As a result, ADYNOVATE is longer-acting and was developed for intravenous replacement therapy or prophylaxis on a less frequent basis than standard regimens in adult and adolescent patients with hemophilia A. The proposed indications include

treatment and control of bleeding episodes and routine prophylaxis in adolescents and adults.
To support licensure for the proposed indications, the clinical development program for ADYNOVATE included data from a non-randomized open-label 2-arm treatment study evaluating efficacy, safety and PK where Previously Treated Patient (PTP) subjects age 12 and above with severe Hemophilia A received either a prophylactic regimen of 45 IU/kg twice weekly (Arm A, n = 121) for at least 50 exposure days (ED) or six months (whichever was longer), or an on-demand dosing regimen using doses ranging from 10 to 60 IU/kg (Arm B, n = 17) for at least six months. A safety and efficacy study in pediatric subjects less than 12 years of age is now ongoing, but had not enrolled any subjects at the time of BLA submission. In the BLA, data for subjects less than 12 years was provided for a very limited number of subjects. Thus the safety, efficacy, and pharmacokinetic profiles of ADYNOVATE have not been established in pediatric patients less than 12 years old.

A total of 159 previously treated patients (PTPs) were enrolled in the study and 138 subjects were used for the Full Analysis Set (FAS) of safety and efficacy in the treatment phase. There were a total of 17 adolescents age 12 to less than 16 years and 121 adults age 16 to 65 years in the FAS. All subjects were male with the majority being White (75.4%) or Asian (23.9%). Overall, ADYNOVATE was effective in prophylactic and on-demand dosing in adolescent and adult hemophilia A subjects.

Demographics and baseline characteristics were similar in both treatment arms with the exception of a higher percentage of zero target joints at screening in subjects in the prophylaxis arm (32% in the prophylaxis arm vs. 12% in the on-demand arm). The mean number of target joints per subject was 1.60 in the prophylaxis arm and 2.18 in the on-demand arm. Of the 121 prophylaxis subjects, 21 were previously managed on an on-demand regimen prior to the study whereas all 17 on-demand subjects had never received prophylaxis. There were no entry criteria for the minimum number of bleeding episodes for subjects in either arm. (The historical annualized bleeding rate (ABR) in patients with severe hemophilia A typically ranges between 20 to 50 or more bleeding episodes per year.) Using a negative binomial model to estimate ABR, the mean [median] ABR in the treatment analysis population set or safety analysis set (SAS) population was 4.3 [1.9] in the prophylaxis arm (N=120) and 43.4 [41.9] in the on-demand arm (N=17). Thus the use of routine prophylaxis in the dosage and frequency prescribed was associated in this trial with a 90% reduction in the mean ABR compared to the rate observed during on-demand therapy. This difference in the mean ABR between treatment arms was statistically significant ($p < 0.0001$). The hypothesis test for the primary efficacy endpoint required statistically significant ($p<0.5$) results in ratio of the ABR in the prophylactic arm compared to the ABR with episodic treatment in the on-demand treatment arm. This study met statistical significance for the primary efficacy assessment. Notwithstanding the higher percentage of subjects with zero target joints in the routine prophylaxis arm and the somewhat lower number of mean target joints per subject in that arm, this reviewer concluded that differences in baseline characteristics and demographics in the two treatment arms were insufficient to introduce major bias in the study efficacy outcomes and would not explain the 90% lower ABR in the routine

prophylaxis arm vis-à-vis the on-demand treatment arm. This conclusion was reinforced by the results of subgroup analyses according to target joint status at baseline and whether subjects had previously used routine prophylaxis, all of which consistently demonstrated a substantially lower ABR in the routine prophylaxis subgroups.

The elimination half-life of ADYNOVATE is 14.3 hours compared to an average half-life of 8-12 hours in non-fusion protein plasma-derived or recombinant FVIII products. The mean dose per prophylaxis infusion was 44.4 IU/kg with a median dosing interval of 3.6 days. Of the subjects who received routine prophylaxis, ninety-three percent reduced their pre-study FVIII dosing frequency by 30% or more when compared to the on-study frequency. Additionally, 70.4% of subjects in the prophylactic arm were able to reduce the frequency of dosing from their pre-study prophylactic treatment regimens by at least one less prophylactic infusion per week after switching to ADYNOVATE for prophylaxis. Nevertheless, it bears mention that twice-weekly dosing remains within the range of existing routine prophylaxis regimens recommended for other [non-fusion protein] Antihemophilic Factor (Human) products.

A total of 591 bleeds were treated during the ~6 month efficacy evaluation period with 361 bleeds recorded for on-demand subjects and 230 bleeds for subjects in the prophylaxis arm. Eighty-five percent of the total bleeds required one infusion, 11% required 2 infusions and 4% required 3 or more infusions. Of the 120 subjects on prophylaxis, 38% experienced no bleeds. In contrast, in the on-demand arm, zero% of subjects experienced no bleeds. For each bleeding episode, subjects were asked to rate the efficacy of ADYNOVATE on a 4-point scale from excellent (four points) to no response (one point). The percent of the bleeding episodes not rated for efficacy was 0.5%. Of rated bleeding episodes, 95.2% were rated as excellent or good, 3% as fair and 1.2% as no response.

The adverse event profile of ADYNOVATE was most commonly headache (2%), nasopharyngitis (2%), upper respiratory infection (1.3%), arthralgia (1.3%) and back pain (0.7%).

FVIII inhibitor formation was not observed during the pivotal study. Seven subjects who tested negative at screening developed transient IgG antibodies against FVIII or PEG-FVIII at 1 visit or 2 consecutive study visits after exposure to ADYNOVATE. Antibodies were transient and not detectable at subsequent visits or at completion of the study. None of the 137 subjects included in the SAS developed a persistent binding antibody response against FVIII, PEG-FVIII, PEG or CHO proteins during the study. Nine subjects showed pre-existing antibodies against FVIII, PEG- FVIII or PEG prior to first exposure to ADYNOVATE. A risk assessment analysis was performed by the sponsor and demonstrated no clinically significant adverse events, lack of therapeutic effect, or alterations in pharmacokinetics. This reviewer agrees with the sponsor's risk assessment analysis concerning the lack of clinically significant adverse reactions and the absence of instances of lack of therapeutic effect. The potential consequences of an immune reaction can range from development of binding antibodies without any clinical significance to rare but severe life-threatening conditions, including allergic reactions.

The benefit to risk profile for ADYNOVATE remains favorable despite the seven subjects with transient binding antibodies to FVIII as the inhibitor assays performed on subsequent samples were negative and there was no observed clinical significance.

Recommendation:
An approval is recommended.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

All subjects were male.
The median age was 23 years.

Table 1: Demographic and baseline data

Mean (SD) and Median (Min ; Max) Age in Years of Subjects by Treatment Arm in FAS						
Subgroup	**Total**		**Prophylaxis**		**On-Demand**	
All	30.0 (12.34) 29.0 (12 ; 58)	N=138	29.8 (12.53) 28.0 (12 ; 58)	N=121	31.5 (11.05) 32.0 (13 ; 56)	N=17
12 to < 18 years	14.5 (1.58) 15.0 (12 ; 17)	N=25	14.5 (1.53) 15.0 (12 ; 17)	N=23	15.0 (NA) NA (13 ; 17)	N=2
18 to 65 years	33.4 (10.96) 31.0 (18 ; 58)	N=113	33.4 (11.18) 30.0 (18 ; 58)	N=98	33.7 (9.7) 32.0 (19 ; 56)	N=15

Race and Ethnicity of Subjects by Treatment Arm in FAS		
	Prophylaxis (N=121) n (%)	**On-Demand (N=17)** n (%)
Race		
Asian	27 (22.3%)	6 (35.3%)
Black or African American	1 (0.8%)	0 (0%)
White	93 (76.9%)	11 (64.7%)
Other	0 (0.0%)	0 (0.0%)
Ethnicity		
Hispanic or Latino	6 (5.0%)	0 (0%)
Not Hispanic or Latino	115 (95.0%)	17 (100.0%)

[Source: Adapted from BLA 125566 Clinical Study Report, Page 79-80]

The ratio of ABR among routine prophylaxis group adolescent subjects (n = 15) divided by the corresponding value among on-demand adolescent subjects (n = 2) subjects was 0.17, and was not statistically significant (p = 0.06). The inconclusive results were due to limitations of statistical power with only 2 adolescents subjects included in the analysis for the on-demand arm. The PK results obtained in adolescents and adults were comparable. The mean ABR in the prophylaxis group of adolescent subjects was similar to the mean ABR in the prophylaxis group of adult subjects. Thus, based on the ABR and PK results in these age groups, it is reasonable to conclude that efficacy for routine

prophylaxis to reduce the frequency of bleeding episodes in adolescent and adult age groups is comparable.

Within the racial subgroups, the ratio of mean ABR among Whites in the prophylaxis arm to that in the on-demand arm was 0.07 (95% CI: 0.04 – 0.15). Among Asians, the ratio of mean ABR in the prophylaxis arm to that in the on-demand arm was 0.22 (95% CI: 0.08 – 0.62). There were no black subjects in the on-demand arm and only one in the prophylaxis arm. The latter subject had a mean ABR of 1.8.

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

2. Clinical and Regulatory Background

There are numerous rFVIII products licensed for marketing, none of these are PEGylated rFVIII products. Please refer to section 2.2 for a detailed list of FDA approved products available for the treatment of Hemophilia A. These products have been approved in adults and children with Hemophilia A for the control and prevention of bleeding episodes, perioperative management of bleeding and routine prophylaxis to reduce the frequency of bleeding episodes and the risk of joint damage. (The language of the indications varies somewhat between licensed products.)

The development of activity-neutralizing antibodies (inhibitor) to a FVIII product is the main safety concern across this class of products. Previously untreated patients (PUPs) are at higher risk of developing inhibitors.

Although regulatory decisions for approval of these products are generally based on studies in previously treated patients, the FDA evaluates the safety data from previously untreated patients when available to further assess the immunogenicity and safety of these products.

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia A is a rare hereditary blood disorder caused by deficiency or dysfunction of Factor VIII resulting in bleeding secondary to abnormal clot formation. The hemophilia A gene is located on the X chromosome with an X-linked recessive inheritance pattern and spontaneous gene mutation in 30% of cases, affecting 1 in 10,000 male births and rare females.

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

Treatments for hemophilia A require replacement with a form of Factor VIII. Factor VIII treatments include human plasma derived and recombinant Factor VIII preparations which are the mainstay of therapy. FDA-approved recombinant Factor VIII products include Helixate (CSL Behring distributed form of Kogenate FS), Kogenate FS (Bayer (b) (4)), ADVATE, Recombinate, Refacto and Xyntha. There are also multiple approved plasma derived Factor VIII products including: Alphanate, Humate-P and Hemofil M.

2.3 Safety and Efficacy of Pharmacologically Related Products

ADYNOVATE a fusion protein consists of a full length form of recombinant antihemophilic factor ((b) (4) to the marketed recombinant Antihemophilic Factor product (ADVATE), covalently conjugated to a polyethylene glycol (PEG) reagent. ADVATE was FDA approved in 2003. Safety concerns as stated in the prescribing information for ADVATE include hypersensitivity and Factor VIII inhibitors. ADVATE is indicated for the control and prevention of bleeding episodes, perioperative management and routine prophylaxis to prevent and reduce the frequency of bleeding episodes.

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

Human subjects were exposed for the first time to this product under the current IND.

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

The evidence for safety and efficacy for this product was collected under IND 15299.

A pre-IND meeting (CRMTS#6990) was held on May 14, 2009. The purpose of the meeting was to discuss the chemistry, manufacturing and controls (CMC) and the pre-clinical development program.

A pre-IND meeting (CRMTS#8603) was held on September 19, 2012, to discuss a proposed protocol that included a comparative study of at least two prophylaxis doses (Protocol 261303) and the sponsor's future plans for pediatric and surgical studies. The clinical development plan included a completed Phase 1 study (Protocol 261101), a Phase 2/3 study in PTPs ≥12 years, with > 150 EDs (Protocol 261201), a pediatric study in

PTPs < 12 years of age (Protocol 261202), a surgery study in at least 5 subjects with at least 10 major surgeries (Protocol 261204), a study in PUPs (Protocol 261203) and a Continuation Study to obtain at least 100 EDs in at least 200 subjects was planned (Protocol 261302). The FDA found the clinical development program to be reasonable.

A Phase 2/3, Multi-center, Open Label Study of Efficacy, Safety, and Pharmacokinetics of ADYNOVATE Administered for Prophylaxis and Treatment of Bleeding in PTPs with Severe Hemophilia A was included in the IND submission on December 26, 2012. No clinical comments were conveyed to the sponsor following FDA review of this submission (Protocol 261201).

A Phase 3 Prospective, Uncontrolled, Multi-center Study Evaluating Pharmacokinetics, Efficacy, Safety and Immunogenicity of ADYNOVATE in Previously Treated Pediatric Patients (<12 years of age) with Severe Hemophilia A was submitted to the IND on March 10, 2014. No clinical comments were conveyed to the sponsor following FDA review of this protocol.

On October 8, 2013, a written request to a meeting request (CRMTS#9063) was provided. Key agreements regarding the clinical issues included agreements that:

1) No additional clinical analyses of the data obtained from the biochemical analyses [that] support comparability of ADVATE Bulk Drug Substance (BDS) manufactured at the (b) (4) manufacturing sites would be required.
2) Cross-reference of the ADVATE BLA to support the ADYNOVATE BLA filing was acceptable.
3) Four dosage strengths (250, 1000, 2000 IU/vial) may be licensed since the majority of the clinical data was obtained using the 500 and 1000 IU/vial, provided CMC specifications were met.

On March 25, 2014 a pre-BLA meeting (CRMTS#9324) was held to discuss CMC, pre-clinical and clinical issues. Key agreements regarding the content of the BLA submission were reached regarding the following clinical issues: the statistical analysis plan, the completed studies (Protocol 261201 and 261101) that were necessary to support the BLA, the studies to be included in the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) and the proposed language to the dosing and labeling section with regard to targeting trough levels and limiting dose. The sponsor was notified that:

1) They were required to submit a pediatric assessment with data to support the safety and efficacy in pediatric subjects 12 to < 18 years.
2) To support a labeled claim of perioperative management, safety and efficacy data from at least 10 subjects undergoing 10 major surgical procedures.
3) A planned action to address safety concerns was required

On March 28, 2014, FDA communicated with the sponsor as a follow up to CRMTS#9324, that the sponsor's plan to provide data from the pivotal study (Protocol #

261201) to support the safety and efficacy in pediatric subjects ≥ 12 -18 years of age was acceptable.

An initial pediatric study plan (iPSP) was submitted on December 11, 2013. FDA provided additional comments following which a revised iPSP and a deferral request for studies in subjects less than 12 years of age was submitted on March 10, 2014. Following review of this submission, FDA agreed to the revised iPSP and notified the sponsor that a pediatric assessment to support the efficacy and safety of this product in pediatric subjects 12 to < 18 years would be required in the BLA submission.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was sufficiently organized to perform a complete clinical review without unreasonable difficulty. The submission consisted of five modules in the Common Technical Document Structure.

3.2 Compliance With Good Clinical Practices and Submission Integrity

CBER Bioresearch Monitoring issued inspection assignment for one foreign and two domestic clinical investigator study sites participating in the pivotal trial. Inspection outcomes did not reveal significant problems that impacted clinical data submitted to BLA 125566/0.

Protocol Deviations

Protocol deviations were categorized as major or minor in accordance with ICH E3.

There were 41 major deviations, summarized as below.

One subject assigned to the prophylactic arm treated himself as if on on-demand therapy and therefore discontinued.

Seven cases of incorrect administered prophylactic dose ; of these a majority received higher doses. Five cases were treated with the incorrect product (ADVATE in lieu of ADYNOVATE). Four cases of administration of incorrectly stored product. One subject received treatment for <50 EDs before the end of treatment. One subject who received on-demand treatment was assigned to the prophylactic arm.

There were six cases of missed study visits, two cases of study-related procedures performed prior to obtaining informed consent, one case had procedures performed prior to eligibility confirmation, one subject had PK assessments performed prior to washout period, and one subject had PK assessment done prior to at least 50 EDs.

Six cases were related to study procedures not being done, four cases were related to procedures being performed as specified in a subsequent protocol amendment prior to

obtaining informed consent and two subjects did not receive at least 50 EDs prior to the end of treatment visit.

Comments: These deviations undermine the rigor of the trial data, but do not impact the conclusions from this study.

3.3 Financial Disclosures

Covered clinical study : Study # 261101 and Study # 261201 (pivotal study)		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 72		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 5 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Financial certification and disclosure information (Form 3454) have been submitted for both US and Non-US sites.

Of the 5 investigators who had disclosable financial arrangements, four investigators received grant support for conducting another study for the applicant. Of these four investigators, two received grants totaling (b) (4), (b) (6) through a research grant provided by

Baxter (to the affiliated academic research program), one investigator received a grant of (b) (4), (b) (6) and another investigator received a grant of (b) (4), (b) (6) Japanese Yen. One investigator received compensatory benefit while serving on an advisory board for Baxter. Study sites affiliated with these investigators were Sites 105, 110, 112, 236

Reviewer Comments: The grant supports to the four investigators were indirectly related to compensation for the studies under review. Therefore the risk to data integrity for this study does not appear to be substantial. Therefore additional sensitivity analysis excluding these sites was not performed.

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

4.1 Chemistry, Manufacturing, and Controls

ADYNOVATE (Antihemophilic Factor, Recombinant, PEGylated) is an extended half-life ($T_{1/2}$) recombinant human coagulation factor VIII (Antihemophilic Factor (Recombinant); rFVIII) modified with polyethylene glycol (PEG) and expressed in Chinese Hamster Ovary (CHO) cells. The mean number of PEG moieties per rFVIII molecule is (b) (4) ADYNOVATE is manufactured using Baxter's Antihemophilic Factor (Recombinant) which is also the active substance in Baxter's licensed product ADVATE. ADYNOVATE is manufactured by covalently binding a branched PEG reagent with a molecular weight of 20 kDa to ADVATE. No human or animal materials are employed during the manufacturing process of ADYNOVATE.

Chemical modification with PEG is a well-established method to improve the pharmacokinetic (PK) profile by extending $T_{1/2}$ and circulation of therapeutic proteins. PEGylation using high molecular weight polyethylene glycols (>10 kDa) is an important tool employed to increase the size of therapeutic proteins. While PEGs with a molecular weight of <30 kDa would be expected to be excreted via the kidney, PEGylated rFVIII has a molecular weight of approximately 280 kDa which exceeds the size for renal clearance. The clearance of endogenous FVIII occurs through interaction with low density lipoprotein receptor-1 (LRP-1), primarily in the liver. PEGylation of rFVIII alters the interaction with LRP-1 by decreasing receptor-binding capacity, although binding affinity remains unaffected. As a result, PEGylation may extend FVIII $T_{1/2}$ due to reduced binding of the PEG conjugated FVIII to LRP-1 for liver clearance.

The purification process includes integration of a virus inactivation step (solvent/detergent (S/D) treatment). The potency (in international units, IU) is determined using an *in vitro* one-stage clotting assay against the World Health Organization (WHO) International Standard for factor VIII concentrate.

The final product is a sterile, non-pyrogenic, preservative-free, lyophilized preparation for intravenous (IV) injection.

4.2 Nonclinical Pharmacology/Toxicology

Please see Pharmacology/Toxicology review memo for complete details. Per this review, the submitted nonclinical studies and resulting data are sufficient to establish the pharmacological and clotting activity of ADYNOVATE.

The effects of ADYNOVATE were evaluated in through a cross-over study designed to evaluate increasing doses of ADYNOVATE or another approved recombinant human FVIII product. Dosing of these hemophilic mice with ADYNOVATE at doses approximately equivalent to the human starting dose restored the ex vivo whole blood clotting time (WBCT) activity and activated partial thromboplastin time (aPTT) to within normal limits. No serious adverse effects or evidence of thrombogenicity were reported.

Studies with PEG-FVIII in FVIII replete monkeys did not demonstrate elevations in ex vivo biomarkers of thrombosis at doses up to 12 fold greater than the maximum ADYNOVATE clinical dose.

4.3 Clinical Pharmacology

Pharmacokinetics
Please refer to the Clinical Pharmacology review memo for complete details. The pharmacokinetics of ADYNOVATE were evaluated through two studies designed to compare ADYNOVATE to ADVATE in PTPs with severe hemophilia. The PK results from the two studies were acceptable. The PK parameter differences between the one-stage and chromogenic assays were less than 20% and did not appear to be of clinical significance. The estimated mean clearance in adolescents age 12 to < 17 years of age was similar to the mean clearance in adults aged 18 – 58 years of age. Although a shorter mean terminal half-life and lower estimated mean in-vitro recovery (IVR) were noted adolescents compared to adults, these differences are not expected to impact dosing recommendations.

4.4 Statistical

A total of 137 subjects in the treatment analyses population group or safety analysis set (SAS) were treated with ADYNOVATE. The mean ABR ratio for the prophylaxis vs on-demand group is 0.1 (95% CI: 0.06. 0.19) and estimated success rate for treatment of bleeding expressed as a proportion was 0.96 (95% CI: 0.91, 0.98). The study met success criteria for efficacy.

4.5 Pharmacovigilance

The analyses of the safety data did not identify safety issues in the use of ADYNOVATE for the treatment of bleeding episodes, long-term use in adolescents and adult PTPs with severe hemophilia.

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

The data used in the review of this BLA were based on the clinical data provided in BLA 125566.

5.1 BLA/IND Documents that Serve as the Basis for the Clinical Review

Documents pertinent to the review of this submission were provided in BLA 125566/0 and IND 15299. Specifically, all items in the Clinical Study Reports Section 5 of the BLA were reviewed including patient narratives as well as the safety update amendment submitted 31 March 2015 and all subsequent clinical and prescribing information amendments.

5.2 Table of Studies/Clinical Trials

The completed, in-progress, and planned post-marketing clinical trials are summarized in the Tables below adapted from BLA 125566/0 Clinical Overview.

Table 2 Listing of Studies in the ADYNOVATE Clinical Development Program

Study Number	Short Study Title and Description	Study Status Report	Sample Size	Main Inclusion Criteria	Dose Range and Frequency
261101 (Trial #1)	Dose Escalation Study Phase 1, first-in-human study to evaluate the safety PK parameters of a single dose ADVATE followed by ADYNOVATE	Complete	19	PTPs, 18-65 years, FVIII<1%	Cohort 1: 30 IU/kg BW of ADVATE followed by the same dose of ADYNOVATE after a wash-out period Cohort 2: 60 IU/kg BW ADVATE followed by the same dose of ADYNOVATE after a wash-out period. Acute bleeding episodes were treated with ADVATE.
261201 (Trial # 2)	Multi-center Phase 2/3, open-label two-arm study, to evaluate the safety and PK parameters	Complete	138	PTPs, 12-65 years, FVIII<1%	Prophylaxis: 45±5 IU/kg BW for >50 EDs or 6 months (whichever occurs last) On demand: 10-60 ±5 IU/kg for approximately 6 mo Acute bleeding

Study Number	Short Study Title and Description	Study Status Report	Sample Size	Main Inclusion Criteria	Dose Range and Frequency
					episodes were treated with ADYNOVATE. PK: ADVATE and ADYNOVATE
261202	Phase 3, uncontrolled pediatric study to study efficacy, safety, immunogenicity and PK	Ongoing	60 2 - <6 yrs: 30 6 - < 12yrs: 30	PTPs <12 yrs, FVIII<1%	Prophylaxis: 50±10 IU/kg BW over a period of 6 months or at least 50 EDs. Acute bleeding episodes were treated with ADYNOVATE. PK: ADVATE and ADYNOVATE
261204	Surgery, Phase 3, multi-center, open-label study in surgery and other invasive procedures	Ongoing	50 major and minor surgeries, ~ 40 subjects to ≥ 10 major surgeries/invasive procedures in ≥ 5 subjects	PTPs, 2-75 years, FVIII<1%	Dosed to target FVIII levels of 80-100% of normal for major surgeries, and 30-60% of minor surgeries
261302	Continuation, Phase 3b, multi-center, continuation study of safety and efficacy in the prophylaxis of bleeding	Ongoing	250	PTPs who have received ADYNOVATE	Prophylaxis: Dose and frequency based on previous treatment or PK guided to maintain trough levels >3% for a minimum of 100 EDs
261203	PUPs, Phase 3 multi-center study, to evaluate safety and immunogenicity	Planned	110 (100 evaluable)	PUPs < 6 yrs, FVIII <1% with ~ 3EDs pre-study with other FVIII products	Prophylaxis: 30±5 to 45±5 IU/kg of ADYNOVATE once or twice weekly
261303	PK guided prophylaxis, Phase 3, open-label, multi-center study to compare PK guided regimen targeting three different FVIII trough levels	Planned	116 to have 96 evaluable subjects (48 per treatment arm)	PTPs who completed prior ADYNOVATE study or are naïve 12-65 years FVIII <1%	PK guided to maintain trough levels of 1-3% (ADYNOVATE twice weekly) or 10 (±2)% (ADYNOVATE every other day)

[Adapted from BLA 125566/0 Clinical Overview]
PTPs – subjects with hemophilia A who have been treated with FVIII product previously.
EDs – Exposure days
PUP – previously untreated patient
IU – International Unit
[Source: BLA 125566/0 Clinical Overview]

5.3 Consultations

No consultations were requested by the clinical team.

5.4 Advisory Committee Meeting

An Advisory Committee Meeting was not held. Although ADYNOVATE is a new molecular entity for coagulation products, addition of the PEG moiety is well-established in FDA regulatory review. A BPAC waiver was submitted.

5.5 External Consults/Collaborations

External consultation was not obtained

5.6 Applicable Literature

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Johnson, K.A. & Zhou, Z-Y. Cost of care in Hemophilia and Possible Implications of Health Care Reform. ASH Education Book (2011), 413-418. *American Society of Hematology, http://asheducationbook.hematologylibrary.org/content/2011/1/413.full.pdf*

Rossbach, H-C (2010). Review of antihemophilic factor injection for the routine prophylaxis of bleeding episodes and risk of joint damage in severe hemophilia A. *Vasc Health Risk Manag*, 6, 59-68.

6. Discussion of Individual Studies/Clinical Trials

A brief discussion of the studies regarding the clinical study design and outcomes relevant to the assessment of efficacy and safety is provided below.

6.1 Trial #1

Pharmacokinetic Study, ADYNOVATE in Subjects with Hemophilia A

Brief Summary: A phase 1, first in human study to assess the safety and PK of ADYNOVATE in PTPs aged 18 to 65 years with severe hemophilia A was conducted in Europe and Japan. The mean $T_{1/2}$ was 1.4- and 1.5-fold higher for ADYNOVATE compared to ADVATE in Cohorts 1 (30 IU/kg) and 2 (60 IU/kg), respectively, demonstrating an extended half-life for ADYNOVATE. Antibodies to FVIII were assessed by ELISA pre-infusion and post-infusion and any positive samples were assayed for the presence of inhibitory antibodies. No subjects developed inhibitory antibodies to FVIII or binding antibodies to PEG after a single infusion.

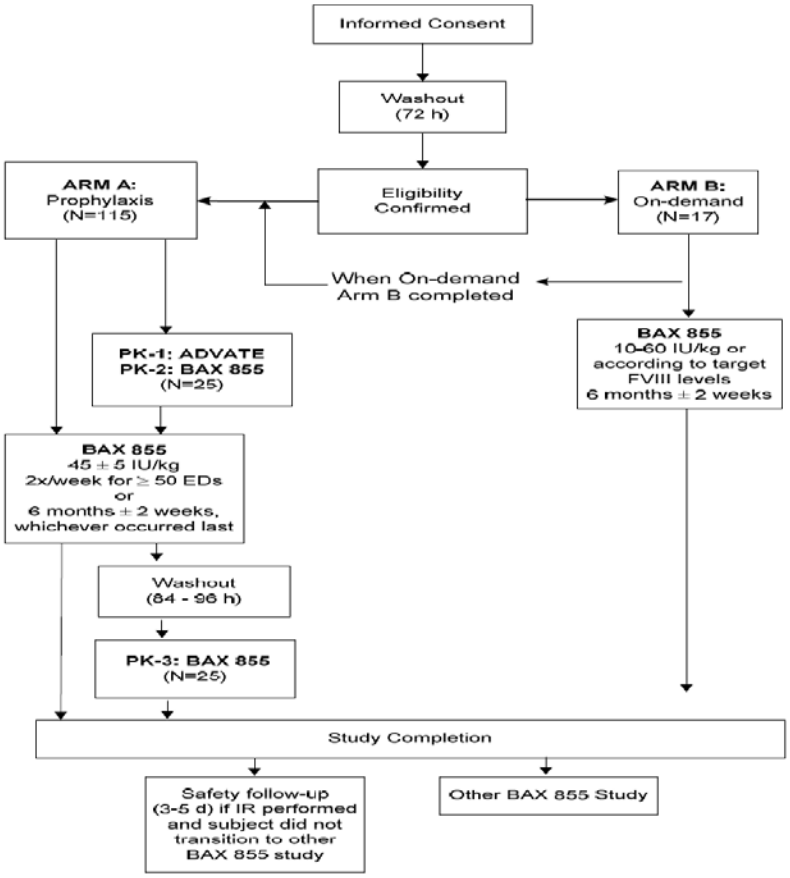
6.2 Trial #2

Pivotal Safety and Efficacy Study of ADYNOVATE in Subjects with Hemophilia A

A schematic of the pivotal trial design is depicted in the figure below.

Figure 1: Schematic of the Design Trial #2

Study Design for Baxter Clinical Study 261201



[Source: BLA 125566/0 Full Clinical Study Report; ADYNOVATE]

Reviewer comment: The design of Trial #2 is adequate to meet the trial objectives.

6.2.1 Objectives (Primary, Secondary, etc)

Primary Objective:
The objective of the pivotal study was to evaluate the PK, safety and efficacy of ADYNOVATE in adolescent and adult subjects with hemophilia A. Safety was assessed in terms of notable changes from baseline laboratory values, incidence of adverse events and inhibitor formation, while efficacy was determined by number of bleeding episodes with ADYNOVATE per subject annualized over the study period (i.e. comparison of prophylactic Arms A versus on-demand Arm B), as well as the hemostatic response to administration of the product for bleeding episodes.

The detailed primary objectives of the trial were as follows:

- To compare the annualized bleeding rates (ABR) between subjects who received a prophylactic dosing regimen with those who received an on-demand regimen

Secondary objectives:

- To determine the immunogenicity of ADYNOVATE (Inhibitory antibodies to FVIII; Binding antibodies (IgG and IgM) to FVIII, PEG-FVIII, and PEG; Anti-CHO antibodies)
- To determine the safety of ADYNOVATE as assessed by occurrence of AEs and changes in vital signs and clinical laboratory parameters following ADYNOVATE administration
- To determine the PK parameters of ADYNOVATE following initial and repeat administrations after at least 50 EDs compared to PK parameters of ADVATE. (Primary PK parameters: Plasma half-life ($T_{1/2}$); Mean residence time (MRT); Total body clearance (CL); Incremental recovery (IR))
- To estimate the rate of success of ADYNOVATE for treatment of bleeding episodes
- To characterize ADYNOVATE for treatment of bleeding episodes through the number of ADYNOVATE infusions needed for the treatment of a bleeding episode and through the length of intervals between bleeding episodes
- To compare the total weight-adjusted consumption of ADYNOVATE for each regimen
- To assess changes from baseline in the following patient-reported outcome measures (PROs): Bleeding and pain severity as measured using the Haemo-SYM questionnaire and health related quality of life (HRQoL) as assessed using the SF-36 questionnaire

Exploratory objectives:

- To assess health utility, using the EuroQol-5 dimensions (EQ-5D) assessment tool, patient satisfaction, patient activity levels and health resource use, over time for subjects receiving ADYNOVATE

Reviewer comment: The primary objective of comparing the efficacy of prophylactic to on-demand therapy is consistent with the general approach to evaluation of this class of products. The comparison of pharmacokinetic and pharmacodynamic parameters of the investigational product to an approved product is consistent with prior regulatory approaches to evaluation of efficacy of this class of product.

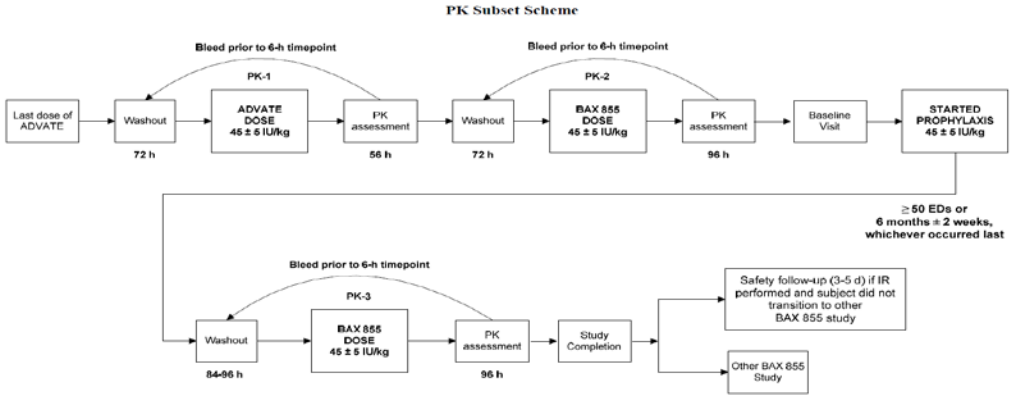
6.2.2 Design Overview

The treatment phase of the trial was a phase 2/3 open-label, non-randomized design intended as the pivotal study for licensure. A minimum of 150 EDs to a factor VIII preparation was a pre-enrollment requirement for a planned enrollment of 132 with approximately 119 anticipated evaluable adolescent and adult male PTPs with severe hemophilia A.

The choice of prophylaxis or on-demand treatment depended on the subject's previous history of FVIII treatment regimen. The first 17 subjects previously treated on-demand were enrolled into the on-demand arm and the subsequent subjects previously treated

with on-demand treatment were assigned to the routine prophylaxis arm, as were all subjects previously treated with routine prophylaxis. After signing the consent form, all subjects were treated with ADVATE either on-demand only or for routine prophylaxis until the screening procedure was completed and the PK or efficacy portions of the trial commenced. There were two treatment arms in the study and a subset of 25 subjects in the routine prophylaxis arm underwent initial and repeat PK evaluation. ADVATE was used as a comparator to ADYNOVATE in all subjects in the PK subgroup of the study. Subjects first received ADVATE in PK-1 followed by ADYNOVATE in PK-2. ADYNOVATE was further re-assessed (PK-3) after completing at least 50 exposure days in order to evaluate whether the PK properties remained consistent

Figure 2 PK Subset Scheme



[Source: BLA 125566/0 Full Clinical Study Report; ADYNOVATE]

Arm A subjects received a twice weekly prophylaxis dose of 45 ± 5 IU/kg to ensure that a majority of subjects maintained FVIII levels above 1% at all times. Duration of prophylaxis was ≥ 50 EDs (N=115 subjects planned), or 6 months ±2 weeks, whichever occurred last. Prophylactic dosing was administered twice weekly, at 3day, 4 day, or 3.5 day intervals.

Arm B was an on-demand treatment arm with suggested dose ranges consistent with the proposed ADYNOVATE prescribing information and international guidelines (10 to 60 ± 5 IU/kg) for an approximate duration of 6 months (N=17 subjects planned). One additional infusion to maintain hemostasis when given within 48 hours after bleed resolution was also acceptable.

The planned sample size for the treatment study phase was 115 subjects on prophylaxis and up to 17 subjects using an on-demand schedule.

Treatment response for bleeding episodes was assessed by individual subjects using a four-point efficacy rating scale. Efficacy was pre-defined as a response of good or excellent. The definitions for each rating are described in the table 1 below and include at least one objective criterion.

Table 3: Efficacy Rating Scale for Treatment of Bleeding Episode.

Rating	Description
Excellent	Full relief of pain and cessation of objective signs of bleeding (e.g., swelling, tenderness and decreased range of motion in the case of musculoskeletal hemorrhage) after a single infusion. No additional infusion is required for the control of bleeding. Administration of further infusions to maintain hemostasis would not affect the scoring
Good	Definite pain relief and/or improvement in signs of bleeding after a single infusion. Possibly requires more than 1 infusion for complete resolution.
Fair	Probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution
None	No improvement or condition worsens.

Bleeding episodes in the prophylaxis group were also treated with ADYNOVATE. Rescue therapy with ADVATE was permissible if an inadequate response to on-demand therapy with ADYNOVATE was observed, as assessed by the subject and/or his physician.

FVIII activity trough levels were to be measured at each study visit (baseline, week 2 ± 5 days and week 4 ± 1 week, after 10 to 15 EDs, month 3 ± 2 weeks, and at study completion/termination) after an adequate wash-out period of at least 84 to 96 h following the previous infusion of ADYNOVATE and of at least 72 hours following the infusion of ADVATE. Trough levels were generally only assessed in prophylaxis subjects, and were optional in on-demand subjects, as they could not always be adequately planned.

All FVIII activity blood samples were to be analyzed using the one-stage clotting assay as the primary assay while the chromogenic assay was performed as supportive data. FVIII antigen was measured using an enzyme-linked immunoabsorbent assay (ELISA). Von Willebrand factor (VWF) antigen for the pre-infusion sample only in PK subset was measured using an (b) (4) assay.

Inhibitory antibodies to FVIII were measured by the (b) (4) Bethesda assay at each study visit. All testing was done at the central laboratory in one batch. The overall study duration was 78 weeks and subjects were given the option to continue treatment with ADYNOVATE in the extension study.

6.2.3 Population

Requirements for this trial included males aged 12 years or older with severe (FVIII activity $\leq$1%) hemophilia A. Subjects also had at least 150 prior exposure days with a FVIII product. A total of 121 subjects in the prophylactic cohorts (Arm A) and 17 subjects in the on-demand group (Arm B) entered the dosing phase of the study, but one

subject assigned to the ADYNOVATE routine prophylaxis group never received ADYNOVATE and was instead treated with ADVATE throughout the trial.

Reviewer comment: The selection of the population is representative of the target population with severe hemophilia.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The planned prophylaxis regimen was an intravenous 45 IU/kg dose of ADYNOVATE twice weekly (Arm A) for a period of six months or for at least 50 exposure days, whichever came later. Changes in dose and frequency, whenever clinically indicated, could be made at the discretion of the investigator, but there were specific criteria in the protocol for raising the routine prophylaxis dose to 60 IU/kg twice weekly if subjects (a) had two target joint bleeds in a consecutive two month period or (b) had a single non-target joint bleed or (c) had a trough FVIII level < 1% and the investigator concluded they were at increased risk of bleeding as a consequence. Subjects in the on-demand group (Arm B) were treated with ADYNOVATE at doses ranging from 10-60 IU/kg depending on the type and severity of the bleeding episode.

6.2.5 Directions for Use

The anticipated intravenous doses for prophylaxis were 45 $\pm$ 5 IU/kg. On-demand treatment regimens were based on international recommendations for licensed FVIII products with doses ranging from 10-60 IU/kg.

6.2.6 Sites and Centers

The trial was a multi-investigator, multicenter, international study. A total of 159 male subjects were enrolled at 72 investigational sites worldwide.

6.2.7 Surveillance/Monitoring

The safety of this study was reviewed by a clinical dosing committee and study management team at the subject level. Safety was also monitored by an independent data and safety monitoring committee (DSMC), composed of six experts in the field of hemophilia clinical care and research who met at least annually at specified time points for data review as well as on an as needed basis. The trial's screening assessments are provided below in Table 4. Physical examinations, medical histories, and concomitant medications were assessed. Adverse events were recorded in subject diaries and reviewed at each visit.

Table 4 Schedule of Assessments

Schedule of Study Procedures and Assessments													
Procedures/ Assessments	**Screening Visit[a]**	**PK Subset (PK-1/PK-2)[b]**			**Study Visits**					**PK Subset (PK-3)[c]**			**Completion/ Termination Visit[e,m] 6 Mo ± 2 Wk**
		Pre-Infusion	**Infusion**	**Post-Infusion**	**Base-line Visit**	**2 Wk ± 5d**	**4 Wk ± 1 Wk**	**After 10-15 EDs[d]**	**3 Mo ± 2 Wk**	**Pre-Infusion**	**Infusion**	**Post-Infusion**	
Informed Consent[f]	X												
Eligibility Criteria	X												
Medical History	X												
Concomitant medication & non-drug therapy[g]	X	X	X	X	X	X	X	X	X	X			X
Physical Exam	X[h]				X	X	X	X	X	X			X
Vital Signs	X				X	X	X	X	X	X		X	X
Adverse Events[g]		X	X	X	X	X	X	X	X	X	X	X	X[j]
Hand out Subject Diary	X												
Review and Discuss Subject Diary		X		X	X	X	X	X	X	X		X	X
Bleeding Episodes and Treatment[g]	X	X		X	X	X	X	X	X	X		X	X
Laboratory Assessments[i]	X	X		X	X	X	X	X	X	X		X	X
IP Treatment[j]			X		X	X	(X)	(X)	X		X		(X)[k]
PROs[l]					X								X

Note: This schedule represents Protocol Amendment 3 and Protocol Amendment 4. Most subjects were treated according to Amendment 1 (Refer to Protocol Amendment 1 Section 21.2).

a. The screening visit procedures, including laboratory evaluations, were to be completed within 45 days prior to the first infusion of BAX 855 (or ADVATE for subjects participating in the PK substudy).

b. Pre and post infusion blood draws for PK-1 over a period of 56 hours (within 30 minutes prior to and at 10 (± 5) min, 0.5 h (± 5 min), 1 h (± 5 min), 3 h (± 30 min), 6 h (± 30 min), 9 h (± 30 min), 24 h (± 1 h), 32 h (± 2 h), 48 h (± 2 h), and 56 h (± 4 h)) following an infusion of 45 ± 5 IU/kg of ADVATE after a wash-out period of at least 72 hours and for PK-2 over a period of 96 hours (within 30 min pre-infusion and at 10 min (± 5 min), and 0.5 h (± 5 min), 1 h (± 5 min), 3 h (± 30 min), 6 h (± 30 min), 9 h (± 30 min), 24 h (± 1 h), 32 h (± 2 h), 48 h (± 2 h), 56 h (± 4 h), 72 h (± 4 h), and 96 h (± 4 h) post-infusion) following the infusion of 45 ± 5 IU/kg of BAX 855 following a washout period of at least 72 to 96 hours in subjects participating in the PK subset.

c. Pre and post infusion blood draws over a period of 96 hours (within 30 min pre-infusion and at 10 min (± 5 min), and 0.5 h (± 5 min), 1 h (± 5 min), 3 h (± 30 min), 6 h (± 30 min), 9 h (± 30 min), 24 h (± 1 h), 32 h (± 2 h), 48 h (± 2 h), 56 h (± 4 h), 72 h (± 4 h), and 96 h (± 4 h) post-infusion) following the infusion of 45 ± 5 IU/kg of BAX 855 (PK-3) after a washout period of at least 84 to 96 hours. The timepoint of the last post-infusion blood draw, 96 hours following infusion of BAX 855, coincided with the Completion/Termination Visit, in case there was no bleed. Otherwise, the Completion/Termination was to be performed after at least 84 to 96 hours elapsed since the most previous administration of BAX 855 to treat the bleeding episode.

d. For subjects receiving prophylactic treatment, the Week 4 and the 10-15 EDs Visits were permitted to be combined if they fell within 2 weeks of each other. If combined, all study procedures as detailed for the Week 4 Visit should have been performed. For subjects being treated on-demand only, the 10-15 EDs Visit was allowed to be combined with any other visit that fell within 2 weeks of reaching 10-15 EDs. In that case, the visit with the more comprehensive assessments was to be followed.

[e] The Completion/Termination visit was to take place after the subject had accumulated ≥50 EDs or 6 months ± 2 weeks of prophylactic treatment, whichever occurred last, or 6 months ± 2 weeks of on-demand treatment.
[f] Written Informed Consent must have been obtained prior to any study-specific procedure.
[g] Adverse events, medications, non-drug therapies, bleeding episodes and their treatment were to be continuously monitored by the study site and reviewed and discussed with the subject at study visits.
[h] Included assessment of Karnofsky performance score.
[i] For laboratory assessments, see Protocol Amendment 4 version 2014 Feb 07 Section 22.4.
[j] BAX 855 was to be administered at the study site for PK-2, PK-3, at baseline and IR determination for subjects receiving prophylactic treatment at Visit Wk 2 ± 5 days and Visit Month 3 ± 2 Wks. A washout period of 84 to 96 hours was required following the most recent BAX 855 infusion before any clinical laboratory assessments. The determination of IR at the other study visits for subjects receiving prophylactic treatment and at each study visit for subjects receiving on-demand treatment was optional.
[k] IP was to be infused at study site only if an optional End-of-Study Incremental Recovery was performed.
[l] PROs were: assessment of bleed and pain severity as measured using the Haemo-SYM questionnaire and HRQoL as assessed using the SF-36 questionnaire, Health utility as assessed using the EQ-5D, Patient satisfaction/preference with treatment as assessed using the Satisfaction Question Set, Patient activity level, and assessment of health resource use.
[m] A safety follow-up call was to be performed within 3-5 days after this visit for those subjects with an optional IR determination at Completion/Termination and who did not transition into the BAX 855 Continuation Study (protocol 261302) or any other BAX 855 study. The subject was to be questioned regarding the occurrence of adverse events.

[Source: BLA 125566/0 Full Clinical Study Report, Page 47-49]

6.2.8 Endpoints and Criteria for Study Success

Efficacy endpoints included the annualized number of breakthrough bleeding episodes during the efficacy period in the prophylaxis arm compared to the on-demand arm (primary endpoint) and assessment of treatment response on a four-point rating scale by subjects and physicians (secondary endpoint), as well as the number of infusions used to treat bleeding episodes. Safety was determined by reporting of adverse events by subjects and investigators, vital signs, and routine safety laboratory testing. Subjects recorded adverse events in their electronic diaries and were questioned at the scheduled evaluations.

6.2.9 Statistical Considerations & Statistical Analysis Plan

The ADVATE prophylaxis study results were used for the sample size evaluation of the ADYNOVATE study. In the ADVATE prophylaxis study, the mean ABR in the on-demand arm (ITT analysis, N=66 subjects) was 48.9 (SD=21.4). The range of ABRs extended from 13.0 to 120.5. The wide range of ABRs in the on-demand arm suggested that a more conservative approach was needed for sample size estimation. To avoid underestimation, a value of one standard deviation lower was chosen and a mean of 27.5 was assumed. In the same ADVATE study, the mean ABR in the prophylaxis arm (ITT analysis, N=66 subjects) was 3.8 (SD=5.4).

Prophylaxis treatment in this ADYNOVATE trial was considered successful if the upper limit of the 95% CI for the ratio between treatment regimens ($ABR_{prophylaxis}/ABR_{on\text{-}demand}$) did not exceed 0.5 (corresponding to a 50% reduction of the mean ABR compared to the on-demand treatment).

For the secondary efficacy endpoint consisting of the proportion of bleeding episodes treated with ADYNVATE rated excellent or good, the lower bound of the 95% CI had to be above 70% for a successful outcome.

Statistical plans for safety and efficacy included descriptive statistics, calculations of ABR and treatment success (excellent or good efficacy rating) using confidence interval

approaches. Annualized bleeding rates were calculated. Sample size calculations were presented in section 9.7.3 of final clinical study report. The planned sample size for the treatment study phase was 115 subjects on prophylaxis and up to 17 subjects using an on-demand schedule assuming a 10% failed screening and drop-out rate.

6.2.10. Results

6.2.10.1 Populations Enrolled/Analyzed

Inclusion criteria included:

1. Severe hemophilia A (factor VIII activity ≤1%).
2. Male, 12 to 65 years of age
3. Previously treated subjects with a minimum of 150 exposure days to a factor VIII preparation

Exclusion criteria included:

4. History of or currently detectable factor VIII inhibitor ≥0.6 Bethesda units
5. Presence of another coagulation disorder

A total of 159 subjects were enrolled: 138 were treated (treated analysis set); 137 were treated with ADYNOVATE and 1 was treated with ADVATE only); including 121 subjects who were assigned to the prophylactic arm and 17 subjects who were assigned to the on-demand arm. Treatment phase analyses included all subjects who received at least one dose of ADYNOVATE (treated population analysis set and Safety Analysis Set (SAS) population). There were 126 subjects who completed the study.

6.2.10.1.1 Demographics

Overall mean age was 30 years with an age range of 12-65 years with 25 adolescent subjects aged 12-17 years and 113 adults aged 18 to 65 years in the treated analysis population set. All subjects were male with 75% Caucasian, 24% Asian, and 1% Black.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Based on data during the efficacy period from 120 subjects, the mean compliance achieved was 100% for the treatment of bleeding episodes and 85.8% for prophylaxis.

Table 5 Measurements of Treatment Compliance in Subjects who received ADYNOVATE

Treatment	All Subjects N (%)
Prophylaxis	103 of 120 (85.8)
Breakthrough bleeds in prophylaxis	120 of 120 (100.0)
Bleeding episode in On-demand	17 of 17 (100.0)

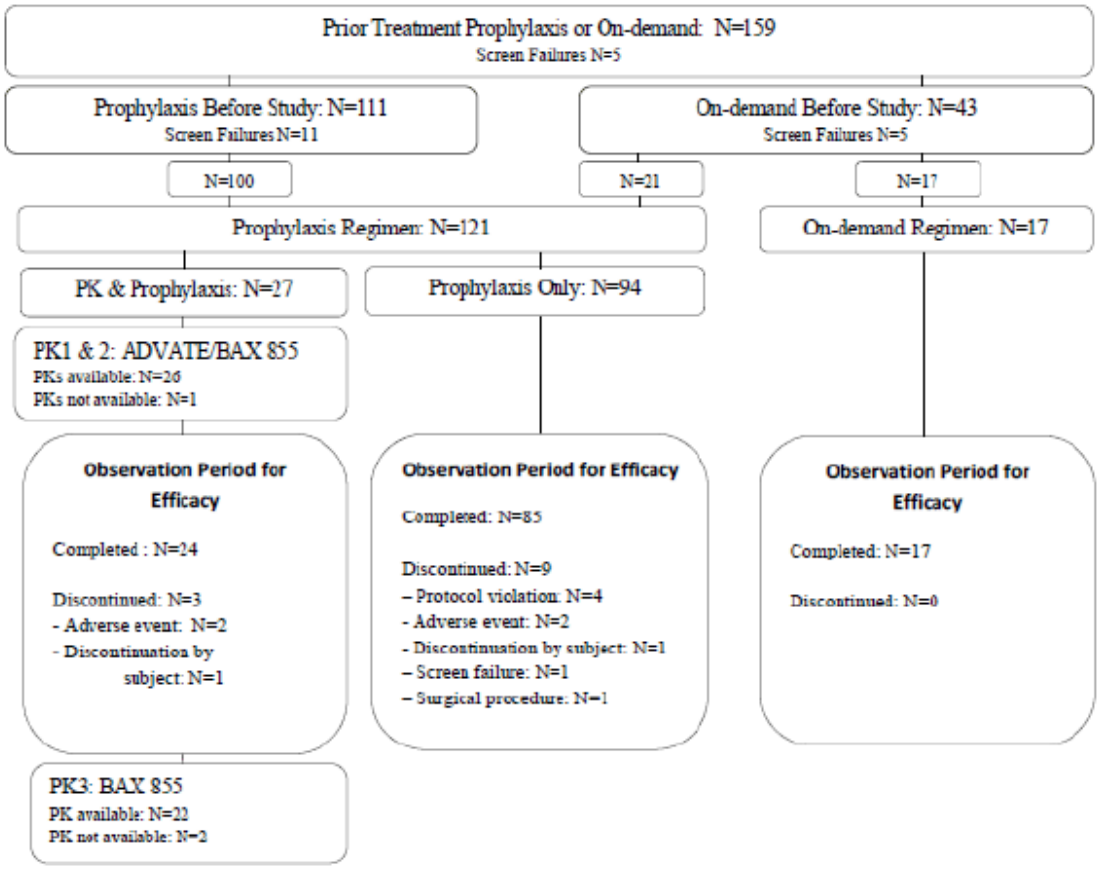
Source: Table 36.
[a]Table 36 was based upon the FAS, in which 121 subjects were assigned to prophylaxis, however, only 120/121 of these subjects were exposed to BAX 855

[Source: BLA 125566/0 Full Clinical Study Report, Page 84]

6.2.10.1.3 Subject Disposition

159 subjects were enrolled. The applicant considered subjects enrolled when they had signed the informed consent form. The full analysis set (FAS) was comprised of 138 subjects who were assigned to either the routine prophylaxis (n = 121) or on-demand treatment groups (n = 17). However, one subject assigned to the routine prophylaxis group received ADVATE throughout the trial and never received ADYNOVATE. The FAS population minus this subject is the safety analysis set (SAS), which will also be referred to a treated analysis population set in this review.

Figure 3 Subject Disposition



[Source: BLA 125566/0 Full Clinical Study Report, Page 77]

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

Routine Prophylaxis

ADYNOVATE was demonstrated to be effective in hemostasis in hemophilia A subjects. The mean unadjusted annualized bleeding rate was 4.7 in the prophylaxis arm compared to a rate of 40.8 in the on-demand arm (See table 4a below). Using a negative binomial regression model, taking into account the fixed effect of regimen (prophylaxis vs. on-demand), stratum (presence or absence of target joints at screening), age at screening as a continuous covariate, and the duration of the observation period for efficacy as an offset,the estimated annualized bleeding rate was in theSAS population was 4.3 in the prophylaxis arm compared to a rate of 43.4 in the on-demand arm (See table 5 below). There was a statistically significant reduction of 90% in the annualized bleeding rate in the routine prophylaxis arm compared to the on-demand arm (analysis of entire safety analysis set/treatment analyses population analysis set cohort).

Table 6 Unadjusted Annualized Bleed Rate by Treatment for ≥12 years of age (Modified ITT – Safety Analysis Set)

Bleeding Episode Etiology	**On-Demand Treatment**		**Routine Prophylaxis Treatment**	
	Median	Mean (SD)	Median	Mean (SD)
Overall	41.5	40.8 (16.3)	1.9	4.7 (8.6)
Joint	38.1	34.7 (15.1)	0.0	2.9 (8.0)
Non-Joint	3.7	6.1 (6.7)	0.0	1.8 (3.0)
Spontaneous	21.6	26.0 (19.6)	0.0	2.9 (7.1)
Traumatic	9.3	14.9 (15.3)	0.0	1.8 (3.1)

Table 7 Unadjusted ABRs by regimen and type of bleed in the per-protocol analysis population are shown below

Bleeding Episode Etiology	**On-Demand Treatment**		**Routine Prophylaxis Treatment**	
	Median (IQR*)	Mean (SD)	Median (IQR*)	Mean (SD)
Overall	41.5 (19.4)	40.8 (16.3)	1.9 (5.8)	3.7 (4.7)
Joint	38.1 (20.1)	34.7 (15.1)	0.0 (2.0)	1.8 (3.0)
Non-Joint	3.7 (7.2)	6.1 (6.7)	0.0 (2.1)	1.8 (3.2)
Spontaneous	21.6 (22.0)	26.0 (19.6)	0.0 (2.2)	2.1 (3.5)
Traumatic	9.3 (25.5)	14.9 (15.3)	0.0 (2.0)	1.6 (2.6)

* Interquartile-range (IQR) is defined as the difference between the 75th percentile (3rd quartile) and the 25th percentile (first quartile)

Prophylactic subjects were dosed at a median dose of 43.58 IU/kg twice weekly (range 41.28 – 46.92 IU/kg) for the treatment duration of 6 months. Subjects in the prophylaxis arm were dosed at an interval of twice weekly and averaged a median interval of 3.56 days (range 3.52 to 3.68 days) during the efficacy period. Demographics and baseline characteristics were relatively similar in both arms with the exception of a higher

percentage of zero target joints at screening in subjects in the prophylaxis arm. Of the 121 prophylaxis subjects in the FAS, 21 were previously managed on an on-demand regimen prior to the study whereas all 17 on-demand subjects had never received prophylaxis. There were no entry criteria for the number of bleeding episodes for subjects in the on-demand arm given the well-established historical annualized bleeding rate (ABR) in patients with severe hemophilia A ranges between 20 to 50 or more bleeding episodes per year. The applicant concluded that ADYNOVATE is effective in reducing bleeding compared to on-demand use when administered as routine prophylaxis at intervals of every 3.5 days in adolescent and adult subjects with hemophilia A. This reviewer agrees with the applicant's conclusion.

Treatment and control of bleeding episodes

For each bleeding episode, subjects were asked to rate the efficacy of ADYNOVATE on a four-point scale from excellent to no response. The percent of the bleeding episodes reported as not rated for efficacy was 0.5%. Of those rated for efficacy, 95.2% were rated as excellent or good, 3% as fair and 1.2% as no response (See table 8).

Table 8 Characteristics of All Bleeding Episodes treated with ADYNOVATE by Bleeding Site and Cause by Age Group (Study 261201: FAS)

Parameter	Category/ Statistics	Units	Site		Cause		All
			Joint[a] n (%)	Non-Joint[b] n (%)	Spontaneous/ Unknown n (%)	Injury n (%)	n (%)
Age Group = All							
# of infusions per bleed	1	Bleeds	391 (85.9)	114 (83.8)	321 (87.2)	184 (82.5)	505 (85.4)
	2	Bleeds	49 (10.8)	15 (11.0)	34 (9.2)	30 (13.5)	64 (10.8)
	3	Bleeds	11 (2.4)	4 (2.9)	11 (3.0)	4 (1.8)	15 (2.5)
	≥4	Bleeds	4 (0.9)	3 (2.2)	2 (0.5)	5 (2.2)	7 (1.2)
Hemostatic Efficacy at 24h	Excellent	Bleeds	176 (38.7)	60 (44.1)	131 (35.6)	105 (47.1)	236 (39.9)
	Good	Bleeds	260 (57.1)	67 (49.3)	221 (60.1)	106 (47.5)	327 (55.3)
	Fair	Bleeds	14 (3.1)	4 (2.9)	9 (2.4)	9 (4.0)	18 (3.0)
	None	Bleeds	4 (0.9)	3 (2.2)	4 (1.1)	3 (1.3)	7 (1.2)
	Not Reported	Bleeds	1 (0.2)	2 (1.5)	3 (0.8)	0 (0.0)	3 (0.5)
Total dose per bleed [IU/kg]	N	Bleeds	455	136	368	223	591
	Mean (Std)	IU/kg	35.7 (23.0)	43.4 (40.3)	35.6 (27.4)	40.5 (29.1)	37.5 (28.1)
	Median	IU/kg	29.2	38.3	29.1	32.8	30.9
	Q1 ; Q3	IU/kg	20.5 ; 45.3	23.6 ; 45.1	21.2 ; 44.6	20.5 ; 47.9	21.2 ; 45.3
	Min ; Max	IU/kg	6.8 ; 257.1	8.4 ; 400.0	6.8 ; 400.0	8.4 ; 257.1	6.8 ; 400.0

[Source: BLA 125566/0 Full Clinical Study Report, Page 457]

6.2.11.2 Analyses of Secondary Endpoints

A total of 591 bleeds were treated during the efficacy period with 361 bleeds recorded for on-demand subjects and 230 bleeds for subjects in the prophylaxis arm. Eighty-five percent of the total bleeds required one infusion, 11% required 2 infusions and 4% required 3 or more infusions (table 5).

Of the 120 subjects on prophylaxis, 38% experienced no bleeds. All 17 on-demand arm subjects experienced bleeds.

No significant differences in the HR QoL were observed over time in the prophylactic arm relative to on-demand subjects between baseline and follow-up. In subjects on prophylaxis, statistically significant improvements between baseline and follow-up were seen only for the physical component score, role physical score, physical functioning score and social functioning score for the SF-36. Overall for all subjects, HR QoL did not show a marked improvement and is considered underpowered and exploratory.

6.2.11.3 Subpopulation Analyses

Adolescent Sub-Study:

Of the 137 subjects included in the safety analysis set (modified ITT population), 25 were 12 to <18 years of age. The baseline characteristics of adolescent subjects were similar to adults with the exception that adult subjects as expected had a greater proportion of target joints and more prevalent arthropathy. The mean clearance in adolescents aged 12 to < 18 years of age was slightly greater than that in the adults. The median elimination half-life of ADYNOVATE in adolescents is 13.14 hours (range 11.21-16.61 hours) which did not differ significantly from the half-life observed in adults. PK results in adolescents obtained at the beginning and end of the study were comparable.

The ratio of ABR among routine prophylaxis group adolescent subjects (n = 15) divided by the corresponding value among on-demand adolescent subjects (n = 2) subjects was 0.17, and was not statistically significant (p = 0.06). The inconclusive results (table 9) were due to limitations of statistical power with only 2 adolescents subjects included in the analysis for the on-demand arm. The small number of adolescent subjects in the on-demand arm also limited other comparisons such as types of bleeding episodes experienced in the two arms.

Table 9 ABR Primary Analysis with Age Subgroups (treated analysis population set)

	Statistics[a]	Prophylaxis	On-Demand	Ratio Prophylaxis/On-Demand	One-sided p-value
All Ages	N	120	17	NA	
	Mean (95% CI)	4.3 (3.4 ; 5.5)	43.4 (25.2 ; 74.8)	0.10 (0.06 ; 0.19)	p <0.0001
Subgroup: 12 to <18 Years	N	23	2	NA	
	Mean (95% CI)	5.0 (3.2 ; 7.7)	39.9 (11.5 ; 138.8)	0.17 (0.04 ; 0.68)	p =0.0630
Subgroup: 18 to 65 Years	N	97	15	NA	
	Mean (95% CI)	4.1 (3.1 ; 5.5)	43.9 (23.9 ; 80.8)	0.10 (0.05 ; 0.19)	p <0.0001

[a] Point estimates for the mean with 95% CI from negative binomial regression model

Analysis of mean ABR by race using the negative binomial regression model yielded a higher point estimate for Asians compared to whites for the ratio for mean ABR in the routine prophylaxis arm divided by mean ABR in the on-demand arm; however, the

confidence interval for the ratio was wide in the case of the smaller Asian subgroup. The ratio of mean ABR among whites in the prophylaxis arm to that in the on-demand arm was 0.07 (95% CI: 0.04 – 0.15). Among Asians, the ratio of mean ABR in the prophylaxis arm to that in the on-demand arm was 0.22 (95% CI: 0.08 – 0.62. There were no black subjects in the on-demand arm and only one in the prophylaxis arm. The latter subject had a mean ABR of 1.8.

Similar to adults, 88% of the total bleeds in adolescents required one infusion, 10% required 2 infusions and 2% required 3 or more infusions.

For each bleeding episode, subjects were asked to rate the efficacy of ADYNOVATE on a 4-point scale from excellent to no response. Overall, there were 96.7% of the bleeding episodes rated as excellent or good and 3.3% as fair.

Age subgroup analyses indicated that ADYNOVATE was effective for on-demand treatment of bleeding episodes in the age range subgroups of 12 to < 18 years and in adults age 18 to 65 years. The point estimates for proportion of bleeding episodes with BAX 855 treatment rated excellent or good for adolescents and adults were:

- 12 to < 18 years subgroup (n = 17): Point estimate 0.97 (95% CI: 0.89; 0.99)
- 18 to 65 years subgroup (n = 64): Point estimate 0.96 (95% CI: 0.90; 0.99)

Race subgroup analyses indicated that ADYNOVATE was effective for on-demand treatment of bleeding episodes in whites and Asians. The proportion of bleeding episodes with BAX855 treatment rated excellent or good were:

- Asian (n=199): Point estimate 0.96 (95% CI: 93.2, 98.7)
- White (n=388): Point estimate 0.96 (95% CI: 93.6, 97.7)
- Black or African American (N=1): Point estimate 1.0,

Table 10 Characteristics of All Bleeding Episodes by Bleeding Site and Cause for Ages 12 - <18 years (FAS)

Parameter	Category/ Statistics	Units	Site		Cause		All
			Joint[a] n (%)	Non-Joint[b] n (%)	Spontaneous/ Unknown n (%)	Injury n (%)	n (%)
Age Group = 12 to <18 years							
# of infusions per bleed	1	Bleeds	48 (87.3)	31 (88.6)	36 (83.7)	43 (91.5)	79 (87.8)
	2	Bleeds	5 (9.1)	4 (11.4)	7 (16.3)	2 (4.3)	9 (10.0)
	3	Bleeds	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	≥4	Bleeds	2 (3.6)	0 (0.0)	0 (0.0)	2 (4.3)	2 (2.2)
Hemostatic Efficacy at 24h	Excellent	Bleeds	7 (12.7)	17 (48.6)	12 (27.9)	12 (25.5)	24 (26.7)
	Good	Bleeds	46 (83.6)	17 (48.6)	29 (67.4)	34 (72.3)	63 (70.0)
	Fair	Bleeds	2 (3.6)	1 (2.9)	2 (4.7)	1 (2.1)	3 (3.3)
	None	Bleeds	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Not Reported	Bleeds	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total dose per bleed [IU/kg]	N	Bleeds	55	35	43	47	90
	Mean (Std)	IU/kg	41.3 (37.2)	42.0 (17.3)	40.7 (19.2)	42.4 (38.8)	41.6 (30.9)
	Median	IU/kg	30.9	38.9	37.6	30.9	33.0
	Q1 ; Q3	IU/kg	29.0 ; 41.5	31.4 ; 48.4	29.1 ; 44.0	30.9 ; 43.7	30.3 ; 43.7
	Min ; Max	IU/kg	14.8 ; 257.1	8.4 ; 87.4	14.8 ; 101.3	8.4 ; 257.1	8.4 ; 257.1

[Source: Adapted from BLA 125566/0 Full Clinical Study Report, Table 26, Page 458]

6.2.11.4 Dropouts and/or Discontinuations

A total of 21 subjects were discontinued from the pivotal study before treatment secondary to screen failure and 12 subjects discontinued after starting treatment for reasons including withdrawn consent, adverse events (see table 11 & 12), and non-compliance.

Table 11 Subjects Discontinued from Trial #2.

Subjects Discontinued From Study 261201	
Reasons for Discontinuation	**N**
Subject had adverse event(s)	4
Subject was non-compliant with the requirements of the protocol, in the opinion of the investigator	4
Other reason	2
Discontinuation by subject	1
Subject required a surgical or dental procedure but did not participate in the surgery study or did not resume participation in this study	1
Screen Failure	1[a]
Source: Table 1. [a]Subject 483001 was assigned to the prophylactic arm (thus was included in the FAS) and received only ADVATE during the screening period.	

Table 12 Reasons for Treatment Discontinuation

The 4 subjects who discontinued treatment in association with an AE are:

Adverse Events Leading to Discontinuation from the Study				
Subject ID	**Preferred Term**	**SAE (Yes/No)**	**Causality (As Assessed by Sponsor)**	**Comments**
108001	Arthralgia	No	Not related[a]	Moderate, recovered/resolved Discontinued after 10 EDs
233001	Muscle haemorrhage	Yes	Not related	Moderate, recovered/resolved terminated the study after 13 EDs
332003	Humerus fracture	Yes	Not related	Severe, recovered/resolved Required terminated the study; discontinued after 25 EDs
400001	Hepatitis C reactivation	No	Unlikely related	Moderate, Recovering/resolving Increase in ALT/AST reported terminated the study; discontinued after 29 EDs

Source: Table 1 and Listing 1 (appendix: Discontinued Patients), Listing 24 and Listing 30 (appendix: Adverse Events)
[a] Assessed as "probably related" by the investigator and unrelated by the sponsor; see sponsor assessment details in Section 12.2.3.2.1

Reviewer Comment: The number of discontinued subjects is within acceptable limits and detailed review of reasons for discontinuation is consistent with the applicant's assessment.

6.2.12 Safety Analyses

6.2.12.1 Methods

Safety of study subjects was assessed in terms of occurrence of AEs and ARs, use of concomitant medication, changes in vital signs and clinical laboratory assessments of hematology, chemistry, lipids, and immunogenicity (inhibitory antibodies to FVIII, binding antibodies to FVIII, PEG, PEG-FVIII, and CHO protein). Only treatment-emergent adverse events (AEs) were analyzed in detail. Immunogenicity testing was performed by ELISA. Although bleeding was monitored and considered an efficacy outcome, subjects were also monitored for development of inhibitors that might predispose to bleeding. The protocol included pre-specified definitions of adverse reactions including severity, seriousness, and relatedness to ADYNOVATE administration. A DSMB monitored the study.

Pre-infusion baseline levels of factor VIII, inhibitory, and non-inhibitory antibodies were also assessed.

6.2.12.2 Overview of Adverse Events

The Safety Analysis Set for trial 261201 included 137 subjects who received at least 1 dose of ADYNOVATE. The summary of exposure is depicted in table 13 below.

Table 13: Summary of Exposure to ADYNOVATE (Trial #2, SAS)

Reason for Treatment	Exposure days [days]	Total IU Infused [IU]	IU/kg Body Mass Infused [IU/kg]	Average IU/kg per Year[a] [IU/kg/year]
Prophylaxis	5940	19,974,295	264,451.84	4397.03
Treatment of Bleeding Episode	697	1,561,048	22,162.31	312.38
Maintenance of Hemostasis	41	94,653	1,336.03	11.96
PK Study	50	173,985	2,274.15	NA
Surgery	2	NA	NA	NA
Total	6717	21,803,981	290,224.33	NA

[a]IU/kg body mass infused divided by the total observation period for efficacy years

[Source: BLA 125566/0 Full Clinical Study Report, Table 32, Page 482]

There was one death considered unrelated to ADYNOVATE (see section 6.2.12.3) and no cases of hypersensitivity reactions including anaphylaxis, inhibitors, or thromboembolic complications.

Four subjects discontinued treatment with ADYNOVATE prematurely due to AEs, of which three were considered unrelated and one was considered unlikely related. The latter subject (40001), a 43 year-old white male with history of prior HCV infection in 2012, discontinued after 29 EDs for treatment-emergent progressive rises in AST and ALT to > 10x the ULN (330 and 730 U/L, respectively) which was attributed to HCV reactivation. HCV (and anti-HBV surface and core) antibody tests were positive at baseline; at an unscheduled visit during the trial, this subject's HCV viral load was extremely high at 25,800,000 RNA IU/mL. The Chinese ovary cell line origin, lack of animal or human protein additives and viral inactivation procedures in the manufacture of this recombinant product would make this SAE extremely unlikely to be product related in the absence of a major breakdown in GMP for which we have no other evidence.

There were 73 subjects (53%) who reported at least 1 AE totaling 171 adverse events throughout the pivotal study. AEs reported at the highest incidence were consistent with common occurrences in the general population including: headache (2%), nasopharyngitis (2%), upper respiratory infection (1.3%), arthralgia (1.3%) and back pain (0.7%). The 3 subjects with headache upon detailed review were found to be non-serious in severity.

There were 8 AEs, experienced by 7 subjects, considered by the investigator as possibly related to ADYNOVATE treatment due to their temporal relationship to administration. The applicant did not agree that 2 AEs of injection site pain were related to the product because a two hour delay elapsed between product infusion and onset of the AEs and because these AEs were associated with the first two infusions but not any subsequent infusions. The sponsor also did not agree that hyperbilirubinemia observed in one subject with a history of stable HCV and resolved HBV infection and whose baseline bilirubin was mildly elevated was related to ADYNOVATE. FDA review concurred with the sponsor's assessment of ARs. The related AEs included 4 cases of headache in 3 subjects (2.2%), flushing, nausea, and diarrhea (each reported in 1 subject [0.7%] each). The flushing was not considered an allergic or hypersensitivity reaction because it was an isolated case that did not reoccur with repeat administration.

Table 14: Related Adverse Events Following ADYNOVATE for All Ages Groups (Trial #2, SAS)

System Organ Class	Preferred Term	Related Adverse Events[a] # of AEs n	# of Subjects N=137 n(%)	AEs per 100 infusions[b] N[c]=6753	AEs per year[d] N[e]=68.3
	Age Group = All				
GASTROINTESTINAL DISORDERS	DIARRHOEA	1	1 (0.7)	0.015	0.015
	NAUSEA	1	1 (0.7)	0.015	0.015
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	INJECTION SITE PAIN	2	1 (0.7)	0.030	0.029
HEPATOBILIARY DISORDERS	HYPERBILIRUBINAEMIA	1	1 (0.7)	0.015	0.015
INVESTIGATIONS	TRANSAMINASES INCREASED	1	1 (0.7)	0.015	0.015
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	ARTHRALGIA	1	1 (0.7)	0.015	0.015
VASCULAR DISORDERS	FLUSHING	1	1 (0.7)	0.015	0.015
All	All	8	7 (5.1)	0.118	0.117

[Source: BLA 125566/0 Full Clinical Study Report, Table 41, Page 542]

There were no patterns of increased consumption or other patterns suggestive of inhibitor formation. Non-neutralizing binding FVIII antibodies were present in 9 subjects (N=137) at screening prior to any dosing, of which two subjects tested positive at each time point throughout the trial. Treatment-emergent non-neutralizing anti-FVIII antibodies developed transiently in 7 subjects at one or two time points during the pivotal study. Transient antibodies were not detectable at subsequent visits or at completion of the study. None of the subjects who had positive inhibitors at any time point demonstrated allergic symptoms or any other concerning symptoms that would likely be related to inhibitor development.

6.2.12.3 Deaths

One subject died 21 days after he discontinued treatment with ADYNOVATE secondary to a diagnosis of neuroendocrine carcinoma and this was appropriately considered unrelated to treatment.

6.2.12.4 Nonfatal Serious Adverse Events

Five SAEs were reported during the study and none were considered possibly related to ADYNOVATE. There were no patterns suggestive of inhibitor formation. The SAEs included osteoarthritis, herpes zoster infection, humerus fracture, muscle hemorrhage secondary to a motorcycle accident and neuroendocrine carcinoma. Clinical review is consistent with the applicant's assessment.

6.2.12.5 Common Adverse Events

The most common adverse events following ADYNOVATE administration were headache (3% of subjects), nasopharyngitis (2%), upper respiratory infection (1.3%), arthralgia (1.3%) and back pain (0.7%). The most commonly reported adverse reactions after ADYNOVATE administration were headache (3%) and nausea (1.2%).

6.2.12.6 Adverse Events of Special Interest (AESI)

Events of special interest included thromboses, hemolysis, and immunogenicity. No case of confirmed inhibitor, thrombosis or hemolysis was detected.

Inhibitory antibodies to FVIII were measured using Bethesda assay. Validated screening and confirmatory ELISA assay was used to detect binding antibodies against CHO, FVIII, PEG-FVIII and PEG. No anti-CHO antibodies were detected during the study.

As noted previously, nine out of 137 subjects demonstrated binding antibodies against FVIII (range in specificity 1:80 to 1:160 titers) at screening prior to dosing, of which tw0 subjects remained positive at each time point throughout the trial. In addition, 7 subjects developed binding antibodies against FVIII during the study. No clinically relevant abnormalities were reported in these subjects. Baxter submitted a comprehensive risk assessment analysis on the formation of these antibodies. The antibody formation was considered transient as subsequent testing at study completion was negative in all subjects.

Subjects with binding antibodies at any time point during the study are described below with titers in Tables 15 & 16.

Table 15: Pre-Existing Binding Antibody Type

Pre-Existing Binding Antibodies At Screening	**FVIII**	**PEG-FVIII**	**PEG**
Subject 1	IgG + (1:80)		
Subject 2		IgG + (1:80) baseline and at 3months	
Subject 3		IgG + (1:80) baseline; lower half-life than average at PK 1&2 but normal at PK 3	
Subject 4		IgG + (1:320)	
Subject 5		IgG + (1:80) screening, baseline (1:160), Week 2 (1:80) and Week 4 (1:80)	
Subject 6		IgG + (1:80) screening, baseline (1:160), Week 2 (1:160), Week 4 (1:160) and after	

		15 EDs (1:80)	
Subject 7		IgG + (1:80) prior to PK1	
Subject 8		IgM+ (1:320)	IgM+ (1:160)
Subject 9		IgM+ (1:160)	IgM+ (1:160)

Binding antibodies to FVIII were detected in 7 subjects at one or more time points during the study but none were neutralizing. None of the subjects with treatment-emergent positive binding antibodies to FVIII remained positive at the time of study completion. Seven subjects had transient positivity for PEG and FVIII at one point during the study but in-depth review of patient narratives for these subjects showed no associated clinical abnormalities.

Table 16: Binding Antibody Type Developing During Study

Binding Antibodies During Study	**FVIII**	**PEG-FVIII**	**PEG**
Subject 1	IgG + (1:80) Week 4		
Subject 2	IgG + (1:80) Week 2		
Subject 3	IgG + (1:80) Week 2		
Subject 4	IgG + (1:80) Week 4		
Subject 5		IgG + (1:160) Week 2	
Subject 6		IgG + (1:80) Week 4 & 3months	
Subject 7		IgG + (1:80) Week 2	

The applicant's conclusion that transient antibodies had no impact on safety and efficacy, no temporal association with adverse events is well supported by the data and risk assessment analysis.

6.2.12.7 Clinical Test Results

There were no patterns of clinically significant laboratory abnormalities that could be ascribed to ADYNOVATE. Similarly, no patterns of abnormal vital signs or physical examination findings were noted.

7. Integrated Overview of Efficacy

7.1 Methods of Integration

No integrated analysis of efficacy is indicated because efficacy data for on-demand treatment of bleeding episodes and routine prophylaxis were submitted only for the single pivotal safety, efficacy, PK, and immunogenicity trial in subjects with severe Hemophilia A age 12 and above.

The safety of ADYNOVATE was evaluated in 169 unique PTPs with severe hemophilia A (factor VIII less than 1% of normal), who received at least one dose of ADYNOVATE in 2 multi-center, prospective, open label clinical studies and 3 ongoing clinical studies. Study subjects consisted of adult (n= 143 with ≥ prior 150 EDs) and pediatric PTPs [(< 6 years of age with ≥ 50 prior EDs (n= 3), ≥ 6 years of age with ≥ 150 prior EDs (n= 23)]. The median duration of participation per subject was 333 (min-max: 1-593) days and the median number of exposure days to ADYNOVATE per subject was 96 (min-max: 1-170).

7.2 Demographics and Baseline Characteristics

For details please see Section 1.1 and Table 1.

7.3 Efficacy Conclusions

ADYNOVATE is effective in subjects 12 years and older for treatment and control of bleeding episodes and routine prophylaxis to reduce the frequency of bleeding episodes.

8. Integrated Overview of Safety

8.1 Safety Assessment Methods

The safety issues of interest were adverse events in general, thrombogenicity and inhibitors. The integrated safety population includes all subjects in all phases. Since all safety assessments were descriptive, no additional methods were required to pool them together.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The pivotal treatment study and initial phase 1 PK sub-study were the completed trials used to evaluate safety. In addition, the ISS submitted 27 March 2015 included an additional 15 subjects treated with ADYNOVATE in the ongoing surgery trial (n = 11 additional individual subjects) and the ongoing pediatric PTP trial (n = 4 subjects). Thus a total of 169 individual subjects were analyzed in the ISS.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The median exposure to ADYNOVATE among these 169 subjects was 96 EDs. Exposure days for children under age 12 were quite limited.

Table 17 Number of subjects for each age group

Age Range	Number of Subjects
< 6 years	**3**
6 to < 12 years	1
12 to < 18 years	25
≥18 years	140

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

Based upon similarities in the subpopulation patient characteristics, it is reasonable to pool the data together as the applicant has done.

8.4 Safety Results

Table 18 lists the adverse reactions reported during clinical studies in ≥ 1% of subjects.

Table 18 Adverse Reactions Reported in ≥ 1% of Subjects

Adverse Reactions Reported for ADYNOVATE			
MedDRA System Organ Class	**MedDRA Preferred Term**	**Number of Subjects n (%) (N=169)**	**Percent per Infusion (N = 13579)**
Gastrointestinal Disorders	Diarrhea	1 (0.6%)	0.01%
	Nausea	2 (1.2%)	0.01%
Nervous System Disorders	Headache	5 (3.0%)	0.06%
Vascular Disorders	Flushing	1 (0.6%)	0.01%

A single AE of blood pressure increase was reported within 24 hours of an infusion but is not included in the above table because of negative rechallenge.

None of the 169 individual (unique) subjects who received at least one infusion of ADYNOVATE developed neutralizing antibodies to factor VIII and no events of hypersensitivity were reported.

Although a persistent binding antibody response was not observed in any of the 169 subjects from all the completed and ongoing studies, 13 total subjects had pre-existing antibodies to factor VIII (n=1), PEG-factor VIII (n=12) and/or PEG (n=3) prior to the first exposure to ADYNOVATE. Additionally, 8 subjects who tested negative at screening developed transient IgG antibodies against factor VIII (n= 5), or PEG-FVIII (n= 3) at one or two consecutive study visits.

8.4.1 Deaths

There was one fatality in the ISS (in the pivotal trial) that was appropriately considered unrelated to ADYNOVATE (neuroendocrine carcinoma).

8.4.2 Nonfatal Serious Adverse Events

There were a total of 16 SAEs (15 nonfatal and 1 fatal) reported in the March 1015 ISS. The 5/137 (3.6%) SAEs reported in the pivotal trial were unlikely related to ADYNOVATE based on detailed review of case reports. These 5 SAEs from trial 261201 are listed as follows:

Table 19 SAE's Unrelated to ADYNOVATE from Trial #2

Subject ID	SAE	Investigator's/Sponsor's Assessment of Relatedness
261201-113005	Osteoarthritis	Unrelated/Unrelated
261201-400002	Herpes zoster infection, neurological	Unrelated/Unrelated
261201-332003	Humerus fracture	Unrelated/Unrelated
261-201-233001	Muscle Hemorrhage	Unrelated/Unrelated
261201-521001	Neuroendocrine Carcinoma	Unrelated/Unrelated

From ongoing trials, the applicant reported in the March ISS 11 additional SAEs for a total of 16 SAEs (9.5%) among 169 subjects across completed and ongoing trials.

Table 20 SAEs from Ongoing Surgery Trial (n = 2/16 (25%))

Subject ID	SAE	Investigator's/Sponsor's Assessment of Relatedness
261204-115001	Abdominal pain	Unrelated/Unrelated
261204-115001	Diabetic Gastroparesis (2 events)	Unrelated/Unrelated
261204-115001	Vomiting	Unrelated/Unrelated
261204-322001	Postoperative Abscess, mild	

Table 21 SAEs in Continuation Trial 261302 (n = 7/125 = 5.6%)

Subject ID	**SAE**	**Investigator's/Sponsor's Assessment of Relatedness**
261201-104003	Pancreatitis, moderate	Unlikely/Unlikely
261201-109001	Pancreatitis, severe	Unrelated/Unrelated
261201-109001	Pneumonia, severe	Unrelated/Unrelated
26201-401001	Splenic Hematoma	Unrelated/Not Associated
26201-401001	Splenic Rupture	Unrelated/Not Associated
261201-483003	Traumatic Fracture	Unrelated/Not Associated

Extension study subject 261201-104003 was a 28 year-old white male who was begun on ADYNOVATE on 19 Aug 2013. He presented to the ER on (b) (6) with a history of 5 days of cramping abdominal pain, vomiting x 1, intermittent nausea, and diarrhea. He was sent home but his epigastric abdominal pain worsened and he was hospitalized on (b) (6) and diagnosed with acute pancreatitis. He had received an infusion of ADYNOVATE the day before he was hospitalized and continued to receive ADYNOVATE infusions in the hospital, due to rectal bleeding. On the day of admission his serum lipase was 1209 U/L and he had a leukocytosis with WBCs 15.8K. The next day his lipase was 244 U/L and his WBCs were 13.7K. A CT scan showed blood in the sigmoid colon. He had recovered and was discharged on the 3rd day of hospitalization. No cause of the acute pancreatitis was identified.

Extension study subject 261201-109001 was a 58 year-old white male with a history of pulmonary hypertension who received his first prophylaxis dose of ADYNOVATE on 13 March 2013. He was hospitalized (b) (6) for pneumonia after having received an ADYNOVATE dose the prior day. Pneumonia resolved with levofloxacin and vancomycin therapy and he was discharged on (b) (6) . This subject was subsequently re-hospitalized for severe acute pancreatitis on (b) (6) 14 after having received ADYNOVATE 2 days prior to hospitalization. The patient's concomitant therapy at the time included Stavudine, Lamivudine, and Etravirine for HIV infection. He was also HCV positive. On the day prior to his hospitalization for acute pancreatitis, he developed abdominal pain which rapidly progressed over 30 min along with sweats, nausea,and dry heaves and weaknesss. He was treated first in the ER that day with odanesetron 4 mg IV which improved his nausea and pain transiently. Pancreatic edema was visible on CT. MRCP showed gallstones and peripancreatic edema. He recovered and was discharged on (b) (6) .

Reviewer Comment: Two cases of acute pancreatitis were diagnosed in two subjects out of 125 subjects who had entered the extension trial as of the data cutoff for the March 2015 ISS. Concomitant therapy with HIV drugs appears to be the most likely cause of

the 2nd case, but the "cluster" finding of 2 cases following ADYNOVATE treatment merits comment. The fact that both cases recovered despite continued administration of ADYNOVATE argues against a causal role of ADYNOVATE in these pancreatitis cases, unless the lots of ADYNOVATE administered following hospitalization were different from the lots administered most recently prior to the development of symptoms of pancreatitis. The applicant was contacted in this regard, but there was ambuigity/incompletess in the records of the specific visit dates these subjects received specific lots of investigational product. Nevertheless, in the absence of an alternative etiology in the first case it was decided to nclude mention of these two cases of acute pancreatitis in the ADYNOVATE package insert.

One SAE in a 15 year-old boy consisted of a splenic hematoma and peritoneal fluid accumulation documented on abdominal ultrasound due to blunt trauma coded as splenic hemorrhage and splenic rupture. This subject was managed non-surgically with bed rest and serial abdominal ultrasound monitoring which revealed a 2 x 1.5 cm splenic defect that was documented to heal completely with observation and daily administration of 46 IU/kg of ADYNOVATE.

8.4.3 Study Dropouts/Discontinuations

A total of 21 subjects were discontinued from the pivotal study after signing of the consent form but before treatment secondary to screening failure, and 12 subjects discontinued after treatment for reasons including withdrawn consent, adverse events (n = 4), and non-compliance.

8.4.4 Common Adverse Events

The most common adverse reactions were headache (3% of subjects) and nausea (1.2% of subjects).

8.4.5 Clinical Test Results

No safety signals were seen in the routine laboratory results, physical examinations, or vital signs. The results of immunogenicity studies are provided in section 12.2.3.3 in the clinical study report.

8.4.6 Adverse Events of Special Interest

Events of special interest included thromboses, hemolysis, and immunogenicity. No episodes of thrombosis, or hemolysis occurred during any part of the trial.

8.5 Additional Safety Evaluations

8.5.1 Immunogenicity (Safety)

There was no pattern of increased consumption of product as evidenced by a consistent average number of infusions and average weight-adjusted consumption per month. The absence of increased consumption and similar IVR and estimated terminal half-life at the start and end of the trial among the PK substudy subjects in the routine prophylaxis arm, in addition to negative modified Bethesda assay immunogenicity assay results, provide evidence against clinically significant immunogenicity mediated by neutralizing antibody against the therapeutic protein. Binding FVIII antibodies that were non-neutralizing were present in 16 subjects out of 137 at both screening prior to dosing and during the pivotal study. None of the 16 subjects showed allergic symptoms or decreased therapeutic effect. One of the subjects had a lower than average half-life at PK assessments 1 & 2 which normalized at PK assessments 3. A risk assessment analysis was performed on these 16 subjects demonstrated no clinically significant adverse events, lack of therapeutic effect or lasting alterations in pharmacokinetics.

8.6 Safety Conclusions

The adverse reaction profile of ADYNOVATE was most commonly headache (3%) and nausea (1.2%).

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Not studied.

9.1.2 Use During Lactation

Not studied.

9.1.3 Pediatric Use and PREA Considerations

The safety, efficacy, and pharmacokinetic profile of ADYNOVATE have not been established in pediatric patients less than 12 years of age. Safety and efficacy were similar between adolescent and adult patients in the pivotal study despite PK parameter differences that included a 70% faster clearance in adolescents compared to the entire PK substudy population. A pediatric pharmacokinetic, safety and efficacy study is ongoing with a planned enrollment of 60 subjects (28 for PK) <12 years of age.

9.1.4 Immunocompromised Patients

Not studied.

9.1.5 Geriatric Use

Not applicable because of younger age of this population. The oldest subject in the pivotal trial was 58 years of age.

10. Conclusions

ADYNOVATE is effective in on-demand treatment and control of bleeding episodes and routine prophylaxis in adolescents and adults with hemophilia A. The applicant's calculations for ABR rates, hemostatic efficacy ratings, and the numbers of infusions used to treat bleeding episodes were reproduced and confirmed by both the clinical and statistical reviewers. The clinical pharmacology reviewer verified the sponsor's calculations of PK parameters. In all 169 subjects for whom safety data were submitted, development of inhibitory antibodies against the product was not observed.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hemophilia A is a rare condition with variable deficiency of coagulation factor VIII. • Hemophilia is accompanied by bleeding into tissues and joints which can be spontaneous, post-traumatic, or perioperative. • Bleeding can be acutely devastating, such as intracranial bleeding, or chronically destructive such as hemophilic arthropathy.	• Hemophilia A is a serious, progressive, life-threatening disease. • The bleeding associated with hemophilia can cause clinically significant complications. • Current treatment is expensive and carries some risks including infection from use of indwelling intravenous catheters and hypersensitivity and other adverse reactions.
Unmet Medical Need	• There are several other recombinant factor VIII product licensed for use by FDA. • Numerous other plasma-derived factor VIII products also exist, but carry the same risks as other human plasma products, such as infection with known or future agents, acute hypersensitivity reactions, or immunogenicity with resistance to therapy.	• Due to convenience and compliance issues, developing products for Hemophilia A replacement therapy that can be effective when given less frequently during routine prophylaxis is desirable. However, Recombinant AHF products that are approved for twice weekly administration for routine prophylaxis already are licensed in the U.S. • Although alternative recombinant therapy exists for Hemophilia A, it is expensive with the average on-demand treatment costing ~$130,000/year and even higher costs for those on prophylactic therapy. Increasing the number of available licensed products could have a positive impact and allow options for hemophilia patients who remain untreated due to high costs; however, there is no guarantee that newer products will be less expensive.
Clinical Benefit	• ADYNOVATE has been shown to be effective for treatment of, and routine prophylaxis to reduce the frequency of spontaneous or traumatic in adolescents and adults.	• ADYNOVATE in a single non-head-to-head phase 3 trial appears equally effective to currently licensed recombinant products.
Risk	• No new risks identified in this BLA.	• The risk of long-term exposure to FVIII products is the development of inhibitory antibodies. Hypersensitivity reactions are expected given sufficiently large population exposure, but none were observed in the clinical trials to date. Overdose with FVIII products might be associated with thrombotic events. None were observed with ADYNOVATE.
Risk Management	• Continue routine postmarketing pharmacovigilance.	• No new risks identified in this BLA.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Summary and Assessment

The formation of FVIII inhibitors was not observed during the pivotal study. Binding FVIII antibodies that were non-neutralizing were present in 16 subjects (N=137) at both screening prior to dosing and during the pivotal study. None of the 16 subjects showed allergic symptoms or decreased therapeutic effect. One of the subjects had a lower than average half-life at PK assessments 1 & 2 which normalized at PK assessments 3. A risk assessment analysis was performed on these 16 subjects demonstrated no clinically significant adverse events, lack of therapeutic effect or lasting alterations in pharmacokinetics. No hypersensitivity or thrombotic events were observed. Two cases of acute pancreatitis appeared to be unrelated to treatment with ADYNOVATE.

Due to the effective hemostasis in treatment and control of bleeding episodes and routine prophylaxis in adolescents and adult subjects with hemophilia A, the benefits of ADYNOVATE are considered to outweigh the risks. Although ADYNOVATE has a somewhat longer half-life (1.4-1.5x) than non-fusion protein marketed rFVIII products, the extent of the practical advantage of this product has yet to be determined given that some of the currently licensed recombinant FVIII, including ADVATE, can also be dosed twice weekly for prophylaxis. The ADYNOVATE pivotal study did show that 93% of the study subjects reduced their pre-study dosing frequency by 30% which was equivalent to one less prophylactic infusion per week (i.e. twice weekly prophylaxis) and this may be of benefit to some patients.

11.2 Discussion of Regulatory Options

The regulatory option discussed is approval of the indications of on-demand treatment and control of bleeding episodes and routine prophylaxis in adolescents and adults with hemophilia A. Formalization of all ongoing studies as PMCs/PMRs, as applicable based on PREA requirements, is also recommended.

11.3 Recommendations on Regulatory Actions

An approval is recommended. Implementation and completion of all postmarketing studies is also recommended. The applicant has agreed to fulfill the following PMR/PMCs:

1) *Phase 3 prospective, uncontrolled, and multi-center study to evaluate PK, efficacy, safety, and immunogenicity of ADYNOVATE in pediatric previously treated patients (PTPs) less than 12 years of age (Study # 261202)***PREA PMR**

2) *Phase 3, prospective, open label multi-center study of efficacy and safety of ADYNOVATE in the perioperative management of bleeding in PTPs age 2-75 years (Study # 261204)***PREA PMR and PMC (The pediatric component included in the PSP would be a PMR; the adult component would be a PMC.)**

3) *Phase 3b, prospective, open label, and multi-center continuation study of safety and efficacy of ADYNOVATE in the routine prophylaxis of bleeding to reduce the frequency of bleeding episodes in PTPs (Study # 261302)***PMC**

4) *Phase 3, multi-center, open label study to investigate safety and immunogenicity of ADYNOVATE in previously untreated patients (PUPs) (Study # 261203)***PMC**

5) *Phase 3, prospective, randomized, open-label multi-center clinical study to compare the safety and efficacy of PK guided ADYNOVATE treatment regimen targeting 2 different FVIII trough levels of 1 - 3% or approximately. 10% (8 - 12%) in PTPs (Study # 261303)***PREA PMR and PMC (The pediatric component included in the PSP would be a PMR; the adult component would be a PMC.)**

Protocols for all of the above studies have been submitted to the IND for this product and have been reviewed by FDA. Anticipated dates for study completion and submission of final complete study reports for the postmarketing studieshave been provided by the applicant in an amendment to this BLA.

11.4 Labeling Review and Recommendations

A labeling review and negotiations with Baxter has been completed, resulting in several changed to the originally proposed draft package insert. A separate labeling review memo has been prepared.