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Review Completion Date / Stamped Date	
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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. Perioperative management of bleeding. Routine prophylaxis to reduce the frequency of bleeding episodes in adolescents and adults with hemophilia A.

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GLOSSARY

ABR	annualized bleeding rate
AJBR	annualized joint bleeding rate
AE	adverse event
BLA	biologics license application
BU	Bethesda unit
BW	body weight
CHO	Chinese hamster ovary
CI	confidence interval
CSR	clinical study report
ED	exposure day
ENR	enrolled set
FAS	full analysis set
FVIII	factor VIII
GHEA	Global Hemostatic Efficacy Assessment
HJHS	Hemophilia Joint Health Score
HRQoL	health-related quality of life
IP	investigational product
IR	incremental recovery
IR	information request
IU	international unit
PEG	polyethylene glycol
PK	pharmacokinetics
PPAS	per protocol analysis set
PRO	patient reported outcome
PTP	previously treated patient
PUP	previously untreated patient
q5d	every 5 days
q7d	every 7 days
rAHF-PFM	recombinant anti-hemophilic factor, plasma/albumin-free method
rFVIII	recombinant factor VIII
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
sBLA	supplemental Biologics License Application
SD	standard deviation

1. EXECUTIVE SUMMARY

ADYNOVATE (BAX855) was approved on 11/13/15 for adolescent (12 years and older) and adult patients with hemophilia A (congenital factor VIII deficiency) for (1) on-demand treatment and control of bleeding episodes, (2) perioperative management, and (3) routine prophylaxis to reduce the frequency of bleeding episodes.

The key labeling changes proposed in this supplemental Biologics License Application (sBLA) include:

- **Dosing and administration for prophylaxis:**
 - (b) (4) [REDACTED]
- **Clinical studies:**
 - long-term prophylaxis experience in pediatric and adult subjects and personalized prophylaxis targeting different FVIII trough levels in subjects ≥ 12 years of age
 - final results of perioperative management use
- **Adverse drug reactions:**
 - include the safety data from the completed clinical studies (e.g., the most common adverse reactions)

To support these labeling changes, the applicant submitted a Prior Approval Supplement (PAS) for ADYNOVATE supported by three completed post-marketing requirement or commitment (PMR/PMC) studies specified in the ANYNOVATE BLA approval letter issued on 11/13/2015. The title of the three studies and their results are summarized as follows:

- **Study 261303** is a phase 3, prospective, randomized, open-label, multicenter clinical study to compare the safety and efficacy of pharmacokinetic (PK)-tailored ADYNOVATE dosing targeting two different factor VIII (FVIII) trough levels. A total of 115 subjects were randomized into two arms (low and high FVIII trough levels). (b) (4) [REDACTED]
- **Study 261302** is a phase 3b, prospective, open label, multicenter continuation study of safety and efficacy of ADYNOVATE in the prophylaxis of bleeding. The primary efficacy outcome measure of the study, spontaneous ABR, was reported for twice-weekly prophylaxis (N=186), fixed-dose prophylaxis every 5 days (q5d) (N=56), fixed-dose prophylaxis every 7 days (q7d) (N=23), and PK-tailored (N=25) as 1.197 (95% CI: 0.918, 1.561), (b) (4) [REDACTED] respectively.

- **Study 261204** is a phase 3, multicenter, open label study of efficacy and safety of ADYNOVATE in previously treated patients with severe hemophilia A undergoing surgical or other invasive procedures. All 24 surgeries (21 major and 3 minor) with available Global Hemostatic Efficacy Assessment (GHEA) scores were rated excellent (100%, 95% CI: 85.8% to 100.0%) and therefore considered a treatment success.

For safety, there were 12 serious adverse events (SAEs) in Study 261303, 52 SAEs in Study 261302 and 4 SAEs in study 261204. Among all 68 SAEs, there was only one SAE was considered related to ADYNOVATE by investigator and sponsor assessment. There was one death occurred during Study 261302, which was considered unrelated to the study treatment.

Overall, this sBLA for ADYNOVATE proposes labeling changes in (1) dosing and administration in prophylaxis, (2) clinical studies, and (3) adverse drug reactions.

(b) (4)

I defer to the clinical reviewer to determine if the totality of evidence supports the other proposed labeling changes.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia A is an X-linked bleeding disorder that occurs predominantly in males and is characterized by deficiency of functional FVIII. 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 FVIII. FVIII treatments include human plasma derived and recombinant FVIII preparations which are the mainstay of therapy.

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

There were seven clinical studies to investigate the long-term efficacy and safety of ADYNOVATE. BLA 125566/0 was approved based on the pivotal study 261201.

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

ADYNOVATE was approved by FDA on 11/13/15.

This sBLA submission, 125566/607, is supported by three completed PMC studies. The clinical study reports (CSR) for the studies were previously submitted as follows: Study 261204 (submitted in 125566/325 on 5/7/17), Study 261303 (submitted in 125566/558 on 10/4/19), and Study 261302 (submitted in 125566/558 on 10/4/19). The PMC requirements they fulfilled in the ADYNOVATE BLA approval letter are as follows:

- The 261204 CSR was submitted to fulfill item 4: *“You have committed to conducting “A 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” [clinical study 261204] – ADULT COMPONENT ONLY.”*
- The 261302 CSR was submitted to fulfill the following two items:
 - Item 3: *“Deferred pediatric study under Pediatric Research Equity Act for routine prophylaxis to compare the efficacy and safety of two different pharmacokinetics (PK) guided dosing regimens in pediatric patients ages 12 to < 17 years (A phase 3, prospective, randomized, multi-center clinical study comparing the safety and efficacy of ADYNOVATE following PK-guided prophylaxis targeting two different FVIII trough levels in subjects with severe Hemophilia A [clinical study 261303] - PEDIATRIC COMPONENT ONLY)”*
 - Item 6: *“You have committed to conducting ‘A phase 3, prospective, randomized, multi-center clinical study comparing the safety and efficacy of ADYNOVATE following PK-guided prophylaxis targeting two different FVIII trough levels in subjects with severe Hemophilia A’ [clinical study 261303] – ADULT COMPONENT ONLY”*
- This 261302 CSR was submitted to fulfill item 5: *“You have committed to conducting “A phase 3b, prospective, open label, and multicenter continuation study of safety and efficacy of ADYNOVATE in the routine prophylaxis of bleeding to reduce the frequency of bleeding episodes in PTPs” age 12 years and above [clinical study 261302].”*

The applicant submitted a major amendment (125566/686) on 9/15/20 in response to FDA’s information request (IR) sent on 9/2/20. The submission 125566/686 updated a few datasets (as well as the corresponding define file) for Studies 261302 and 261303. No previously submitted CSR body, tables, figures and analysis were affected.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

This submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

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

5.1 Review Strategy

Three clinical studies are reviewed in this memo: Studies 261204, 261302, and 261303. Study 261204 provides updated information in perioperative management. Studies 261302 and 261303 provide updated information for prophylaxis data in pediatric and adult subjects.

The applicant proposes to revise clinical trial experience and the adverse drug reactions table in the label to include the data from these three completed clinical studies.

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

This following documents in the sBLA submission 125566/607 were reviewed:

- Module 1
- Module 2.5: Clinical Overview
- Module 2.7: Clinical Summary
- Module 5.2: Tabular-listing-2020apr23-cor-dossier.pdf

The following documents in the sBLA submissions 125566/325 (Study 261204), 125566/454 (Study 261303), and 125566/558 (Study 261302) were reviewed:

- Module 1
- Module 5.3.5.2:
 - Study Report Body
 - Protocol
 - Statistical Analysis Plan
 - ADaM Datasets

The followed documents in the sBLA submission 125566/686 were also reviewed for Studies 261302 and 261303 as a response to FDA's IR sent on 9/2/2020.

- Module 1
- Module 5.3.5.2:
 - Amended ADaM Datasets

5.3 Table of Studies/Clinical Trials

There were seven studies in the clinical development program for this product: 261101, 261201, 261202, 261203, 261204, 261302, and 261303. A summary of all seven studies is provided in Table 1.

Table 1: Listings of Studies in the Clinical Development Program

Study Number	Short Study Title and Description	Study Status Report	Sample Size	Main Criteria for Inclusion	Dose Range and Frequency
261101	ADYNOVATE Dose-escalation Safety Phase 1, first-in-human, prospective, open label, crossover, dose-escalation study to evaluate safety and PK parameters of single doses of ADYNOVATE compared to single doses of ADVATE	Complete CSR 261101	19	PTPs 18 to 65 years FVIII <1%	Two sequential dose cohorts: Cohort 1: Single administration of 30 IU/kg BW of ADVATE followed by administration of the same dose of ADYNOVATE after a wash-out period >96 h Cohort 2: Single administration of 60 IU/kg BW of ADVATE followed by administration of the same dose of ADYNOVATE after a wash-out period >96 h Acute bleeding episodes: treated with ADVATE
261201	ADYNOVATE Pivotal Phase 2/3, multicenter, open label, 2-arm study to evaluate efficacy, safety, and PK parameters of ADYNOVATE and HRQoL	Complete CSR 261201	138	PTPs 12 to 65 years FVIII <1%	Prophylaxis: 45 ± 5 IU/kg BW twice weekly for ≥ 50 EDs or 6 months ± 2 weeks, whichever occurs last On-demand: 10 - 60 ± 5 IU/kg BW for an approximate duration of 6 months Acute bleeding episodes: treated with ADYNOVATE PK evaluation: ADVATE and ADYNOVATE at prophylactic dose level
261202	ADYNOVATE Pediatric Phase 3 prospective, uncontrolled, multicenter study to evaluate PK, efficacy, safety, and immunogenicity of and immunogenicity of ADYNOVATE	Complete CSR 261202	66 2 age groups (32 aged <6 years and 34 aged 6 to <12 years)	PTPs <12 years FVIII <1%	Prophylaxis: 50 ± 10 IU/kg BW over a period of 6 months, or at least 50 Eds Acute bleeding episodes: treated with ADYNOVATE PK evaluation: ADVATE and ADYNOVATE at 60 ± 5 IU/kg

Study Number	Short Study Title and Description	Study Status Report	Sample Size	Main Criteria for Inclusion	Dose Range and Frequency
261204	ADYNOVATE Surgery Phase 3, prospective, open label multicenter study of efficacy and safety of ADYNOVATE in surgical or other invasive procedures	Complete CSR 261204	21 unique subjects who underwent 21 major and 5 minor surgeries; 22 subjects evaluable for safety	PTPs 2 to 75 years FVIII <1%	Surgical prophylaxis: dose tailored to achieve FVIII target levels of 80 - 100% of normal for major and 30 - 60% of normal for minor surgeries
261302	ADYNOVATE Continuation Phase 3b, prospective, open label, multicenter continuation study of safety and efficacy of ADYNOVATE in the prophylaxis of bleeding	Complete CSR 261302	216	PTPs who completed another ADYNOVATE study or ADYNOVATE naïve ≤75 years FVIII <1%	Fixed-dose prophylaxis depending on age, given twice weekly OR PK-tailored prophylaxis to maintain trough FVIII level ≥3% For at least 100 EDs
261303	ADYNOVATE PK-tailored Dosing Phase 3, prospective, randomized, open-label multicenter clinical study to compare the safety and efficacy of PK-tailored ADYNOVATE dosing targeting 2 different FVIII trough levels	Complete CSR 261303	121, 57 in the 1-3% trough arm, 58 in the 10% trough arm, 6 not randomized	PTPs who completed another ADYNOVATE study; or ADYNOVATE naïve; 12 - 65 years of age with FVIII <1%	PK-tailored ADYNOVATE dose to maintain FVIII target trough levels of 1 - 3% or approx. 10% (8 - 12%) FVIII trough level 1 - 3%: approximately twice weekly FVIII trough level approx. 10% (8% - 12%): every other day

Study Number	Short Study Title and Description	Study Status Report	Sample Size	Main Criteria for Inclusion	Dose Range and Frequency
261203	ADYNOVATE PUPs Phase 3, multi-center, open-label study to investigate safety, immunogenicity and efficacy of ADYNOVATE in PUPs (previous untreated patients)	Ongoing	120 (100 evaluable)	PUPs <6 years, FVIII <1%, who have undergone <3 EDs with	Prophylaxis: to be initiated before the age of 3 years or once the subjects has experienced 2 joint bleeds before the age of 3 years, whichever occurs first; at least once weekly dosing of 25 – 50 IU/kg, which may be increased to 80 IU/kg

Source: Adapted from sBLA 125566/607 Module 2: clinical-overview-2020apr15.pdf, Table 1, pages 14-16.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: 261303

6.1.1 Objectives

The primary objective of the study was to compare two prophylactic dosing regimens of ADYNOVATE targeting two different FVIII trough levels, by comparing the proportions of subjects achieving a total ABR of zero in the second 6-month study period.

Secondary objectives included:

- Efficacy
 - To compare the two prophylactic dosing regimens of ADYNOVATE targeting two different FVIII trough levels
 - To determine the hemostatic efficacy of ADYNOVATE in the control of bleeding episodes
 - To evaluate the efficacy of ADYNOVATE for perioperative management, if surgery was required
- Safety
 - To determine the immunogenicity of ADYNOVATE
 - To determine the safety of ADYNOVATE
- Pharmacokinetics
 - To determine the PK parameters of ADYNOVATE at baseline and steady state, if applicable, and the correlation with pre-infusion Von Willebrand factor (VWF) antigen level
 - To determine incremental recovery over time
- Patient Reported Outcomes
 - To assess the difference in the SF-36 physical domain and component change scores from baseline to follow-up between subjects in the 10% trough arm and subjects in the 1-3% trough arm
 - To assess the difference in the change of days of physical activity participation from baseline to follow-up between subjects in the 10% trough arm and subjects in the 1-3% trough arm

6.1.2 Design Overview

This was a phase 3, prospective, randomized, open-label, multicenter study to compare the safety and efficacy of PK-guided ADYNOVATE prophylaxis targeting FVIII trough levels of 1-3% or approximately 10% (8-12%) in adolescent and adult previously treated patients (PTPs) with severe hemophilia A (<1% FVIII). The study was designed to test if the proportion of subjects with zero ABR in the 10% trough level arm is significantly higher than that of the 1-3% trough level arm.

Subjects were screened and randomized (1:1) to one of two dosing regimens: the standard prophylactic dosing arm targeting FVIII trough levels of 1-3%, and the intensified prophylactic dosing arm targeting FVIII trough levels of approximately 10% (8-12%).

The subject's participation was approximately 15-16 months, including a 6 week screening procedure, a 6-8 week period for PK assessments, dose calculation and randomization, and a 12 month treatment period (divided into two 6-month periods).

6.1.3 Population

Inclusion Criteria

For subjects transitioning from another ADYNOVATE study:

- Subject completed the end of study visit of a ADYNOVATE study or was transitioning from the ongoing Baxalta Continuation Study 261302
- Subject was receiving either on-demand treatment or prophylactic treatment with ADYNOVATE and had an ABR of ≥ 2 documented and treated during the past 12 months

For newly recruited subjects:

- Subject was 12 to 65 years old at the time of screening
- Subject had severe hemophilia A (FVIII clotting activity $< 1\%$) as confirmed by central laboratory OR by historically documented FVIII clotting activity performed by a certified clinical laboratory, optionally supported by a FVIII gene mutation consistent with severe hemophilia A
- Subject had been previously treated with plasma-derived FVIII concentrates or rFVIII for ≥ 150 documented exposure days (EDs)
- Subject was receiving either on-demand treatment or prophylactic treatment and had an annual bleeding rate of ≥ 2 documented and treated during the past 12 months
- Subject had a Karnofsky performance score of ≥ 60 at screening

Exclusion Criteria

For subjects transitioning from another ADYNOVATE study:

- Subject has developed a confirmed inhibitory antibody to FVIII with a titer of ≥ 0.6 BU using the (b) (4) Bethesda assay as determined at the central laboratory during the course of the previous ADYNOVATE study
- Subject has been diagnosed with an acquired hemostatic defect other than hemophilia A
- Subject's weight is < 35 kg or > 100 kg
- Subject's platelet count is $< 100,000/mL$

For newly recruited subjects:

- Subject has detectable FVIII inhibitory antibodies (≥ 0.6 BU using the (b) (4) Bethesda assay) as confirmed by central laboratory at screening
- Subject has a history of confirmed FVIII inhibitors with a titer ≥ 0.6 BU (as determined by the (b) (4) Bethesda assay or the assay employed with the respective cut-off in the local laboratory) at any time prior to screening
- Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia A (e.g., qualitative platelet defect or von Willebrand's disease)
- Subject's weight is < 35 kg or > 100 kg
- Subject's platelet count is $< 100,000$ /mL
- Subject has known hypersensitivity towards mouse or hamster proteins, polyethylene glycol (PEG) or Tween 80

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects were screened and underwent an initial PK assessment following a single administration of ADYNOVATE (60 ± 5 IU/kg) to determine PK parameters. After the PK assessment subjects were randomized to one of two dosing regimens: twice weekly dosing to target FVIII trough levels of 1-3% and every other day dosing to target FVIII trough level of around 10% (8-12%). The dose was based on each subject's individual PK. More frequent dosing could be considered if single doses of 80 IU/kg were required or regular FVIII peak levels of 200% would be reached.

6.1.6 Sites and Centers

Subjects were enrolled at 62 study sites in 19 different countries.

6.1.8 Endpoints and Criteria for Study Success

The primary outcome measure is the proportion of subjects with an ABR of zero in the two prophylaxis treatment regimes, in the second 6-month study period. The ABR is calculated as (Observed number of bleeds + Imputed number of bleeds [if the subject prematurely discontinued from the study, the number of bleeds was imputed for the second 6-month period]) / (Period under consideration in years). The period under consideration was 1 year when working with the full year and 0.5 year when working with the second 6-month period (Observation Day 183 to Observation Day 364).

This study was designed to test if there is a significant difference in the primary outcome between the two arms. The null and the alternative hypotheses defined as the following in the SAP:

$$H_0: \text{Proportion Low Level subjects with ABR of } 0 = \text{Proportion High Level subjects with ABR of } 0$$

Versus

H_A: Proportion Low Level subjects with ABR of 0 ≠ Proportion High Level subjects with ABR of 0

Therefore, a p-value less than 0.05 shows the 10% trough arm achieves a significant difference compared with the 1-3% trough arm. A p-value higher than 0.05 means no statistical evidence are collected to support the significant change in the primary endpoint in the 10% trough arm.

Secondary efficacy outcome measures include:

- Total, spontaneous, and traumatic ABR, and spontaneous annualized joint bleeding rate (AJBR).
- Total weight-adjusted consumption of ADYNOVATE.
- Overall hemostatic efficacy rating at 8 (±1) hours after the initiation of treatment and at resolution of bleed. The subject or caregiver rated the overall treatment response at 8 hours after the initiation of treatment and at the resolution of bleed using a 4-point efficacy rating scale: “excellent”, “good”, “fair”, or “none”.
- Number of ADYNOVATE infusions needed for the treatment of bleeding episodes.
- Hemophilia joint health score (HJHS).
- Intra-, post- and perioperative hemostatic efficacy in case of surgery.
- Intra- and postoperative blood loss in case of surgery.

Secondary safety outcome measures include:

- Occurrence of adverse events (AEs) and serious adverse events (SAEs).
- Clinically significant changes in vital signs and clinical laboratory parameters (hematology, clinical chemistry, and lipids).
- Inhibitory antibodies to FVIII, and binding antibodies to FVIII, ADYNOVATE, polyethylene glycol (PEG), and Chinese hamster ovary (CHO) protein.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample size calculation

Assuming 40% of subjects in the 1-3% trough level have zero ABR (based on the pivotal study 261201), and 70% of subjects in 10% trough level have zero ABR, 48 subjects per study group are needed to reject the null hypothesis of no difference between the two study arms against a 2-sided alternative at the 5% level of statistical significance with 80% power. With a 10% drop-out rate, and 10-15% of subjects being non-compliant, approximately 116 subjects total were planned to be randomized between the two ADYNOVATE regimens.

Analysis populations

The all subjects enrolled set (ENR) contains all subjects that signed informed consent.

The Safety Analysis Set (SAS) is comprised of all subjects in the ENR with at least one ADYNOVATE infusion. All safety analyses were planned to be performed on the SAS.

The Full Analysis Set (FAS) is comprised of all subjects who were randomized to one of the two treatment arms and treated prophylactically for any period of time. All efficacy analyses were planned to be performed on the FAS.

The Per Protocol Analysis Set (PPAS) is comprised of all subjects in the FAS who completed the second 6 months of prophylactic treatment and had no major protocol deviations affecting the study results.

The surgery analysis set (SGAS) consists of all subjects in the FAS that underwent some form of surgery (including dental) during the course of their PROPEL participation as recorded on the eCRF.

Primary statistical analysis

The primary endpoints from the two arms were compared through a Chi-squared test with continuity correction at a 2-sided 5% level of significance.

Secondary statistical analysis

For total ABR, spontaneous ABR, traumatic ABR and spontaneous AJBR, separate negative binomial models for bleed rate estimation were used for the second six-month treatment period (Days 183 to 364) as well as for the complete twelve-month treatment period (Days 1 to 364).

For all other outcome measures, descriptive statistics are presented for the two dosing regimens. Point estimates (means and medians) and their 95% CIs were computed.

Missing data handling

For all subjects who prematurely discontinued from the study (i.e., before Day 364), and who refuse to provide data on bleeds for the remaining time till Day 364, the number of bleeds, were imputed for the second 6-month period through subject-specific Poisson models.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 135 subjects were enrolled in the study (signed informed consent) and were included in the ENR set. Seven subjects were screen failures. However, one of the screen-failed subjects erroneously received the PK infusion and is therefore included in the SAS. Another eight subjects discontinued before receiving the PK infusion for determination of the PK-tailored prophylactic regimen. Consequently fourteen subjects were not included in SAS, yielding 121 subjects in the SAS.

A total of 115/135 (85.2%) subjects were randomized, 57 to the prophylactic dosing arm targeting a FVIII trough level of 1-3% and 58 to the prophylactic dosing arm targeting a FVIII trough level of approximately 10% (8-12%). Six of the 121 subjects in the SAS were not randomized: 1 subject was a screen failure (as noted above) and 5 subjects discontinued after receiving the PK infusion but before the first prophylactic dose.

The number of subjects in each analysis set is provided in Table 2.

Table 2: Analysis Populations

	<i>Number of Subjects</i>
ENR	135
SAS	121
FAS	115
Low level treatment arm	57
High level treatment arm	58
PPAS (Per-protocol Analysis Set)	95
Low level treatment arm	52
High level treatment arm	43
SGAS (Surgery Analysis Set)	7
Low level treatment arm	3
High level treatment arm	4

6.1.10.1.1 Demographics

The mean (standard deviation [SD]) age for the 115 randomized subjects was 31.1 (12.95) years (range: 12 to 61 years) and was similar for the 1-3% trough and 10% trough arms at 31.1 (13.76) and 31.2 (12.22) years, respectively. The majority of subjects were White (76/115; 66.1%), 40/57 (70.2%) in the 1-3% trough arm and 36/58 (62.1%) in the 10% trough arm. Thirty-two subjects (32/115; 27.8%) were Asian, 14/57 (24.6%) in the 1-3% trough arm and 18/58 (31.0%) in the 10% trough arm. Seven (7/115; 6.1%) subjects in the FAS were of Hispanic or Latino ethnicity.

The demographic and baseline characteristics are provided in Table 3.

Table 3: Demographic and Baseline Characteristics (FAS)

<i>Parameter</i>	<i>Low Level</i>	<i>High Level</i>	<i>Total</i>
N	57	58	115
Age			
Mean (SD)	31.1 (13.76)	31.2 (12.22)	31.1 (12.95)
Median	29.0	30.5	29.0
Min, max	12, 61	13, 61	12, 61
Weight			
Mean (SD)	70.98 (14.58)	71.92 (15.34)	71.45 (14.91)
Median	72.60	75.00	73.90
Min, max	42.0, 99.7	38.0, 99.8	38.0, 99.8
Height			
Mean (SD)	172.18 (7.242)	172.36 (9.190)	172.27 (8.246)
Median	173.00	174.50	173.00
Min, max	152.0, 191.0	142.0, 186.0	142.0, 191.0
BMI			
Mean (SD)	23.84 (4.183)	24.02 (4.014)	23.93 (4.081)
Median	24.70	24.10	24.50
Min, max	15.5, 34.9	14.7, 32.5	14.7, 34.9
Race			
Asian	14	18	32
White	40	36	76
Other	3	4	7
Ethnicity			
Hispanic	2	5	7
Not Hispanic	53	53	106
Not reported	2	0	2

Source: Adapted from sBLA 125566/558 Module 5.3.5.2: report-body.pdf, Table 5 & 9, page 382-420.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The disease and medical characteristics of the subjects in the FAS are summarized in Table 4.

Table 4: Disease and Medical Characteristics (FAS)

<i>Parameter</i>	<i>Low Level n (%)</i>	<i>High Level n (%)</i>	<i>Total N (%)</i>
N	57	58	115
Gene mutation			
Unknown	47	44	89
Inversion intron 22	5	7	12
Other	7	7	14
Blood group			
A	22 (38.6)	13 (22.4)	35 (30.4)
B	8 (14.0)	9 (15.5)	17 (14.8)
O	19 (33.3)	23 (39.7)	42 (36.5)
AB	3 (5.3)	4 (6.9)	7 (6.1)
Unknown	5 (8.8)	9 (15.5)	14 (12.2)
Number of target joints			
0	17 (29.8)	14 (24.1)	31 (27.0)
1	15 (26.3)	17 (29.3)	32 (27.8)
2	15 (26.3)	13 (22.4)	28 (24.3)
3	5 (8.8)	4 (6.9)	9 (7.8)
≥ 4	5 (8.8)	10 (17.2)	15 (13.0)
Hemophilic arthropathy			
Yes	7 (12.3)	15 (25.9)	22 (19.1)
No	50 (87.7)	43 (74.1)	93 (80.9)
Hepatitis C virus antibody			
Yes	30 (52.6)	26 (44.8)	56 (48.7)
No	25 (43.9)	32 (55.2)	57 (49.6)
Not reported	2 (3.5)	0 (0.0)	2 (1.7)
Hepatitis C virus antibody			
Yes	2 (3.5)	6 (10.3)	8 (7.0)
No	53 (93.0)	51 (87.9)	104 (90.4)
Not reported	2 (3.5)	1 (1.7)	3 (2.6)

Source: Adapted from sBLA 125566/558 Module 5.3.5.2: 261303-report-body.pdf, Table 17 & 9, page 477.

6.1.10.1.3 Subject Disposition

All subjects randomized received at least one prophylactic dose. Nine (9/115; 6.7%) subjects, eight in the 10% trough arm and one in the 1-3% trough arm, discontinued the study prematurely after receiving at least one prophylactic dose: five (3.7%) during the first and four (3.0%) during the second 6-month period of prophylaxis.

In the 1-3% trough arm, one subject (Subject (b) (6)) withdrew after 282 observation days without providing a specific reason.

In the 10% trough arm, eight subjects discontinued prematurely for the following reasons:

- Subject (b) (6) discontinued after 22 observation days due to poor i.v. access and the need to administer prophylactic infusions every 24 h.
- Subject (b) (6) was withdrawn by the investigator after 175 observation days due to poor compliance with e-diary completion, which constituted a major protocol deviation.
- Subject (b) (6) was withdrawn after 82 observation days due to noncompliance with study procedures.
- Subject (b) (6) was withdrawn after 57 observation days due to non-compliance with study procedures.
- Subject (b) (6) was terminated after 124 observation days because of administration of another FVIII product which was a critical deviation.
- Subject (b) (6) was withdrawn by the sponsor after 307 observation days because of non-compliance with study procedures, repeatedly not completing the e-diary.
- Subject (b) (6) withdrew after 190 observation days. The subject refused to renew informed consent.
- Subject (b) (6) was reported as discontinuation by the subject (cannot comply to protocol) in the e-CRF

Overall, one-hundred six (78.5%) of the 135 subjects enrolled completed the study.

6.1.11 Efficacy Analyses

(b) (4)

[Redacted text block]

2 pages have been determined to be not releasable: (b)(4)

(b) (4)

6.1.12 Safety Analyses

6.1.12.3 Deaths

No deaths were observed in this study.

6.1.12.4 Nonfatal Serious Adverse Events

Twelve AEs in 10/121 (8.3%) subjects were serious. One of these SAEs was considered related to ADYNOVATE by investigator and sponsor assessment. This was the development of a transient low-titer FVIII inhibitor (0.6 BU) in a 45-year old Caucasian male in the 10% trough arm. The event resolved within 18 days without changing the subject's dose. The 12 SAEs were evenly distributed between the two prophylaxis arms (6 SAEs in 5 subjects in 1-3% trough arm, 6

SAEs in 5 subjects in 10% trough arm) and also between age cohorts (6 SAEs occurred in pediatric subjects and 6 SAEs occurred in adult subjects).

6.2 Trial #2: 261302

6.2.1 Objectives

The co-primary objectives of the study were:

- To determine the safety of ADYNOVATE based on the incidence of FVIII inhibitory antibody development
- To determine the efficacy of ADYNOVATE based on the ABR of spontaneous bleeding episodes

Secondary objectives in efficacy were:

- To determine the total ABR (spontaneous and traumatic bleeding episodes)
- To determine the overall hemostatic efficacy rating of ADYNOVATE for treatment of breakthrough bleeding episodes
- To determine the length of intervals between bleeding episodes
- To characterize the hemostatic efficacy of ADYNOVATE for treatment of bleeding episodes by the number of ADYNOVATE infusions for treatment
- To determine total weight-adjusted consumption of ADYNOVATE for prophylaxis and for treatment of bleeding episodes
- To assess Patient Reported Outcomes (PROs) over time for subjects receiving ADYNOVATE

Secondary objectives in safety were:

- To determine the safety of ADYNOVATE, as assessed by the occurrence of AEs and changes in vital signs and clinical laboratory parameters
- To determine the immunogenicity of ADYNOVATE

6.2.2 Design Overview

Study 261302 was a Phase 3b, prospective, open label, multi-center study to evaluate the safety and efficacy of ADYNOVATE for prophylactic use and the control of bleeding episodes in subjects with severe hemophilia A. The study includes subjects from other ADYNOVATE studies and ADYNOVATE -naïve subjects.

Subjects could decide to receive either a fixed-dose regimen with ADYNOVATE twice weekly, or a pharmacokinetically tailored (PK-tailored) prophylactic ADYNOVATE dose regimen based on the subject's individual PK to maintain FVIII trough levels of $\geq 3\%$.

Prior to Amendment 4 (5/23/14), depending on their previous regimen and low spontaneous bleeding history during the preceding 6 months, subjects had the option to receive fixed dose prophylaxis every 5 days (q5d) or every 7 days (q7d)

(original protocol dated 6/18/13, Section 8.6.3). While this option was replaced by the option to receive PK-tailored prophylaxis, subjects already on q5d and q7d prophylaxis were allowed to remain on these regimens until completion.

All subjects were to participate in the study until they reached at least 100 EDs.

6.2.3 Population

Inclusion Criteria

Subjects transitioning from other ADYNOVATE studies:

- Subject completed a previous ADYNOVATE study and was willing to immediately transition into this continuation study
- Subject was ≤ 75 years of age at screening of the previous ADYNOVATE study
- Subject continued to have a Karnofsky (for subjects aged ≥ 16 years) or Lansky (for subjects aged <16 years) performance score of ≥ 60

ADYNOVATE-naïve subjects:

- Subject was ≤ 75 years of age at screening
- Subject was naïve to ADYNOVATE
- Subject has severe hemophilia A (FVIII clotting activity $<1\%$) as confirmed by central laboratory at screening after at least a 72-hour washout period
- Subject aged ≥ 6 years had documented previous treatment with plasma-derived FVIII concentrates or rFVIII for ≥ 150 EDs
- Subject aged <6 years had documented previous treatment with plasma-derived FVIII concentrates or rFVIII for ≥ 50 EDs
- Subject was currently receiving prophylaxis or on-demand therapy with FVIII
- Subject had a Karnofsky (for subjects aged ≥ 16 years) or Lansky (for subjects aged <16 years) performance score of ≥ 60

Exclusion Criteria

Subjects transitioning from other ADYNOVATE studies:

- Subject had detectable FVIII inhibitory antibodies (≥ 0.6 BU using the (b) (4) Bethesda assay) as confirmed by central laboratory at screening
- Subject had developed FVIII inhibitory antibodies (≥ 0.6 BU using the (b) (4) Bethesda assay as determined at central laboratory in a previous ADYNOVATE study)
- Subject had acquired a hemostatic defect other than hemophilia A (e.g., qualitative platelet defect or von Willebrand's disease) in a previous ADYNOVATE study
- Subject had severe chronic hepatic dysfunction (e.g., ≥ 5 times upper limit of normal ALT, as confirmed by central laboratory at screening)
- Subject had severe renal impairment (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening

- Subject experienced a life-threatening or gastrointestinal bleeding episode within 3 months prior to study entry.
- Subject was scheduled to use other PEGylated drugs during study participation.

ADYNOVATE-naïve subjects:

- Subject had detectable FVIII inhibitory antibodies (≥ 0.6 BU using the (b) (4) Bethesda assay) as confirmed by central laboratory at screening
- Subject had a history of FVIII inhibitory antibodies (≥ 0.6 BU using the (b) (4) Bethesda assay or the Bethesda assay) at any time prior to screening
- Subject was diagnosed with an inherited or acquired hemostatic defect other than hemophilia A (e.g., qualitative platelet defect or von Willebrand's disease)
- Subject had known hypersensitivity towards mouse or hamster proteins, PEG, or Tween 80
- Subject had severe chronic hepatic dysfunction (e.g., ≥ 5 times upper limit of normal ALT, as confirmed by central laboratory at screening)
- Subject had severe renal impairment (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening
- Subject experienced a life-threatening or gastrointestinal bleeding episode within 3 months prior to study entry
- Subject had current or recent (< 30 days) use of other PEGylated drugs prior to study participation or scheduled use of such drugs during study participation

6.2.4 Study Treatments or Agents Mandated by the Protocol

Subjects could choose one from the following regimens of ADYNOVATE:

- a fixed-dose regimen
 - Subjects aged ≥ 12 years: 45 ± 5 IU/kg twice weekly, which may be increased up to 80 IU/kg
 - Subjects aged < 12 years: 50 ± 10 IU/kg twice weekly, which may be increased up to 80 IU/kg
 - Subjects achieving a sABR = 0 on a twice weekly regimen for 6 months could switch to 30 to 80 IU/kg every 5 days (q5d dosing)
 - Subjects achieving a sABR = 0 on a q5d dosing regimen for 6 months could switch to 30 to 80 IU/kg every 7 days (q7d dosing)
- a PK-tailored prophylactic ADYNOVATE dose regimen based on the subject's individual PK to maintain FVIII trough levels of $\geq 3\%$; the dosing was to be at least twice weekly

6.2.6 Sites and Centers

This study was conducted at 86 sites in 23 countries.

6.2.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint is the spontaneous ABR and the primary safety endpoint is the development of inhibitory antibodies to FVIII (≥ 0.6 BU).

Secondary efficacy endpoints include:

- Total ABR (spontaneous and traumatic bleeding episodes)
- Overall hemostatic efficacy rating as of ADYNOVATE for treatment of breakthrough bleeding episodes (the hemostatic efficacy rating was performed by the subject or caregiver at 24 hours after the initiation of treatment, based on a 4-point rating scale: excellent, good, fair, and none)
- Number of ADYNOVATE infusions to treat bleeding episodes
- Time intervals between bleeding episodes
- Weight-adjusted consumption of ADYNOVATE

Secondary safety endpoints include:

- Occurrence of AEs and SAEs
- Changes in vital signs and clinical laboratory parameters (hematology, clinical chemistry, and lipids)
- Immunogenicity: binding antibodies (IgG and IgM) to FVIII, ADYNOVATE, and PEG; anti-CHO protein antibodies

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Determination

In total, approximately 250 subjects with at least 60 evaluable subjects <12 years of age were planned to be enrolled. The sample size was not based on statistical considerations. Instead, it was based on having 200 evaluable subjects with a minimum of 100 EDs to ADYNOVATE in accordance with the guidance EMA/CHMP/BPWP/144533/2009.

Analysis Sets

The all subjects enrolled set (ENR) contains all subjects that signed informed consent.

The safety analysis set (SAS) is comprised of all subjects in the ENR with at least one ADYNOVATE infusion. All safety analyses are performed on the SAS.

The full analysis set (FAS) is comprised of all subjects in the SAS. Efficacy was analyzed using the FAS.

The per protocol analysis set (PPAS) is comprised of all subjects in the SAS/FAS who had no major deviations from the protocol affecting the study results.

Statistical Analysis Methods

The primary efficacy endpoint, was analyzed using a generalized linear model fitting a negative binomial distribution with a logarithmic link function. Only subjects that had 100 or more EDs were included in the model.

For the primary safety endpoint, the number and proportion (Clopper-Pearson exact 95% CI) of subjects exposed to ADYNOVATE who developed inhibitory antibodies to FVIII (≥ 0.6 BU) was provided.

For secondary efficacy endpoints, the total ABR was estimated and described similarly as the primary efficacy outcome measure. Descriptive statistics were provided for other secondary efficacy endpoints.

Interim Analysis

An interim safety review was to be performed for license submission to the European Medicines Agency (EMA). No formal interim reports were prepared for this study.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Of the 218 enrolled subjects, 216 received at least one prophylactic dose of ADYNOVATE: 215 subjects received at least one dose of ADYNOVATE at a fixed-dose prophylactic regimen and 25 subjects received at least one dose of ADYNOVATE at a PK-tailored prophylactic dose regimen. (Subjects on the twice weekly fixed dose regimen could transition to the q5d or q7d regimens; see Section 6.2.1.) The PPAS includes 186 subjects by excluding 30 subjects who had major protocol deviations from the FAS. Table 8 summarizes the population sizes.

Table 8: Analysis Populations

<i>Population</i>	<i>Number of subjects n (%)</i>
Enrolled subjects	218 (100)
SAS	216 (99.1)
FAS	216 (99.1)
Fixed dose prophylactic	215 (98.6)
twice weekly	186 (85.3)
every 5 days	56 (25.7)
every 7 days	15 (6.9)
PK-tailored prophylactic	25 (11.5)
PPAS	186 (85.3)

6.2.10.1.1 Demographics

For the 216 subjects treated, age at informed consent ranged from 1 to 61 years; the mean (SD) age was 22.8 (15.67) years.

All but one subject who received ADYNOVATE were male (215/216; 99.5%). The only female subject (0.5%) was in the ≥ 6 to <12 years age category. The majority of subjects were White (152/216; 70.4%), followed by Asian (58/216; 26.9%), and Black or African American (4/216; 1.9%). Ten subjects (10/216; 4.6%) were of Hispanic or Latino ethnicity.

The demographic data for the SAS/FAS are provided in Table 9.

Table 9: Demographic Characteristics by Age Group (SAS)

Parameter	Age < 6	[6, 12)	[12, 18)	Age ≥ 18	Total
N	32	33	30	121	216
Age (years)					
Mean (SD)	3.6 (1.29)	7.8 (1.70)	14.2 (1.63)	34.1 (11.47)	22.8 (15.67)
Median	4.0	7.0	14.0	32.0	20.0
Min, max	1; 5	6; 11	12; 17	18; 61	1; 61
Sex					
Male	32	32	30	121	215
Female	0	1	0	0	1
Ethnicity					
Hispanic or Latino	1	2	0	7	10
Not Hispanic or Latino	31	31	30	114	206
Race					
Asian	7	9	5	37	58
Black or African American	1	2	1	0	4
White	22	22	24	84	152
Other	1	0	0	0	1
Mixed	1	0	0	0	1

Source: Adapted from sBLA 125566/454 Module 5.3.5.2: 261302-report-body.pdf, Table 9, pages 77-78.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 10 summarizes the disease characteristics of the SAS subjects.

Ten subjects (10/216; 4.6%), all aged <12 years, were naïve to ADYNOVATE; 206 (206/216; 95.4%) had participated in one or more previous ADYNOVATE studies. The subjects had a mean (SD) of 57.0 (39.62) previous EDs to ADYNOVATE (range: 0 to 277 days).

A total of 110 subjects (110/216; 50.9%) had target joints at screening. The proportion of subjects with target joints and the number of target joints increased

with age. In the <6 years age category, 2/32 subjects (6.3%) had one target joint at screening and none had more than one. In the ≥ 18 years age category, 87/121 subjects (71.9%) had at least one target joint and 22/121 (18.2%) had ≥ 4 target joints.

The overall mean (SD) historical spontaneous ABR was 4.7 (12.58) and was lower in children <6 years (0.1 [0.49]) and ≥6 to <12 years (0.2 [1.39]) than in adolescents ≥12 to <18 years (4.3 [11.32]) and adults (7.2 [15.30]).

A total of 25/216 subjects (11.6%), among them 22 adults, had been on an on-demand regimen prior to the study; the majority of subjects (191/216; 88.4%) had been on FVIII prophylaxis.

Of 216 subjects, 93 (43.1%) had hemophilic arthropathy. The proportion of subjects with hemophilic arthropathy increased with age, amounting to 69.4% (84/121 subjects) in the ≥18 years age category.

Table 10: Disease Characteristics by Age Group (SAS)

<i>Parameter</i>	<i>Age < 6</i>	<i>[6, 12)</i>	<i>[12, 18)</i>	<i>Age ≥18</i>	<i>Total</i>
N	32	33	30	121	216
Previous ADYNOVATE studies participated in					
None	6	4	0	0	10
At least 1	26	29	30	121	206
Previous Exposure Days to ADYNOVATE					
Mean (SD)	47.4 (26.09)	47.5 (18.07)	72.1 (51.62)	58.5 (42.39)	57.0 (39.62)
Median	54.0	54.0	55.0	54.0	54.0
Min, max	0, 105	0, 61	13, 251	3, 277	0, 277
Number of target joints at screening					
0	30	24	18	34	106
1	2	3	6	26	37
2	0	5	3	26	34
3	0	1	2	13	16
≥ 4	0	0	1	22	23
Average spontaneous ABR based on previous 3-6 months					
Mean (SD)	0.1 (0.49)	0.2 (1.39)	4.3 (11.32)	7.2 (15.30)	4.7 (12.58)
Median	0.0	0.0	0.0	0.0	0.0
Min, max	0; 2	0; 8	0; 57	0; 69	0; 69
Treatment regimen prior to current study					
Prophylactic	30	33	29	99	191
On-demand	2	0	1	22	25
Hemophilia arthropathy					
Present	0	2	7	84	93
Absent	32	31	23	37	123

Source: Adapted from sBLA 125566/454 Module 5.3.5.2: 261302-report-body.pdf, Table 9, pages 77-78.

6.2.10.1.3 Subject Disposition

Of the 216 subjects who received at least one prophylactic dose of ADYNOVATE, 29 subjects discontinued the study and 187 subjects completed the study. Table 11 summarizes subject disposition.

Table 11: Subject Disposition

<i>Category</i>	<i>Total (N=218) N (%)</i>
Enrolled subjects	218 (100)
Screen failure	2 (0.9)
Subjects dosed at least once	216
Completed	187 (85.8)
Discontinued	29 (13.3)
Adverse event	5 (2.3)
Physician decision	2 (0.9)
Withdrawal by subject	6 (2.8)
Protocol deviation	6 (2.8)
Death	1 (0.5)
Other	9 (4.1)

Source: Adapted from sBLA 125566/454 Module 5.3.5.2: 261302-report-body.pdf, Table 6, pages 69-70.

During Study 261302, eight subjects (8/216; 3.7%) were transferred at least once to the surgery study (Study 261204) and subsequently returned to Study 261302.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

A total of 186 subjects had 372 spontaneous bleeds on the fixed-dose twice-weekly prophylaxis regimen. The primary efficacy endpoint point estimate (95% CI) for the twice weekly fixed dose regimen was 1.197 (0.918, 1.561).

(b) (4)

[Redacted text block]

Table 12 summarizes the spontaneous ABR for fixed-dose twice-weekly prophylaxis regimen, fixed-dose every 5 days regimen, fixed-dose every 7 days regimen, and PK-tailored regimen. In Table 12, all point estimates and CIs were estimated through generalized linear models fitting negative binomial distributions with logarithmic link functions.

Table 12: Spontaneous/Unknown Annualized Bleeding Rate by Age Group (FAS)

Regimen	Age Group	# of subjects	# of bleeds	Point estimate	95% CI
Fixed Dose Regimen, Twice Weekly at Time of Bleed	All	186	372	1.197	0.918, 1.561
	Age <6	31	43	0.656	0.394, 1.094
	Age ≥6 to <12	31	40	0.762	0.438, 1.325
	Age ≥12 to <18	23	81	1.768	1.093, 2.859
	Age ≥18	101	208	1.259	0.876, 1.812

(b) (4)

Source: Adapted from sBLA 125566/454 Module 5.3.5.2: 261302-report-body.pdf, Table 11, page 86.

6.2.11.2 Analyses of Secondary Endpoints

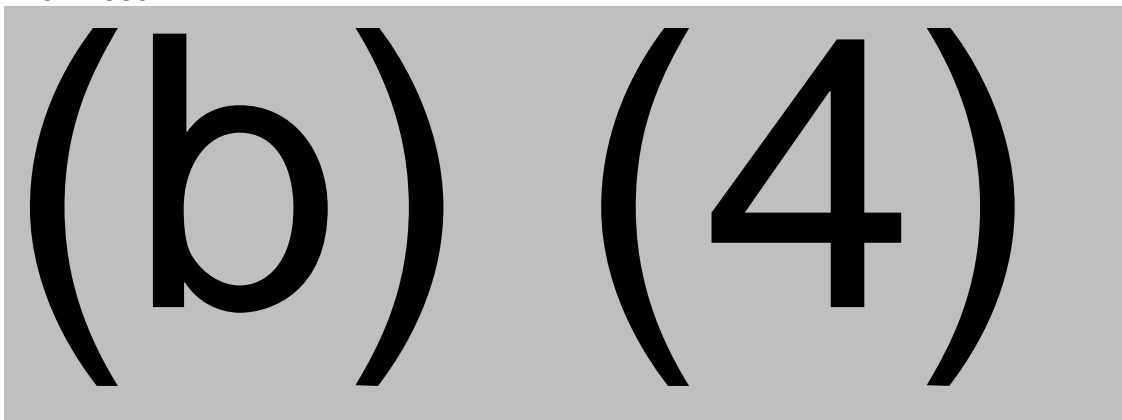
Total Annualized Bleeding Rate

The number of bleeds and total ABR per prophylactic treatment regimen are summarized in Table 13. The total ABR (95% CI) for the fixed-dose twice-weekly prophylaxis was 2.230 (1.852 - 2.686), fixed-dose prophylaxis q5d was (b) (4)

(b) (4) fixed-dose prophylaxis q7d was (b) (4) and PK-tailored regimen was (b) (4)

Table 13: Total Annualized Bleeding Rate (FAS)

Regimen	# of subjects	# of bleeds	Point estimate	95% CI
Fixed Dose Regimen, Twice Weekly at Time of Bleed	186	686	2.230	1.852, 2.686



Source: Adapted from sBLA 125566/454 Module 5.3.5.2: 261302-report-body.pdf, Table 12, page 90.

Similar to Table 12, point estimates and CIs in Table 13 were estimated through generalized linear models fitting negative binomial distributions with logarithmic link functions.

Overall hemostatic efficacy rating of ADYNOVATE for treatment of breakthrough bleeding episodes

A total of 180 of 216 subjects had one or more bleeding episodes during the study. A total of 1064 bleeds occurred (some were reported when the subject was not in any treatment regimen), of which 910 bleeding episodes in 165 subjects were treated and 154 bleeds were not treated with ADYNOVATE. Treatment of 48.1% (438) of these bleeds was rated “excellent”, treatment of 40.4% (368) of bleeds was rated “good”, 5.3% (48) of bleed treatments were rated “fair”, and 0.4% (4) were rated “none”; for 5.7% (52) of bleed treatments no rating was reported.

Number of ADYNOVATE infusions to treat bleeding episodes

The total mean (SD) weight-adjusted dose per infusion to treat a bleed was 44.147 (21.919) IU/kg (median [95% CI]: 44.605 (42.721 - 45.573) IU/kg).

Interval between Bleeding Episodes

The overall mean (SD) interval between bleeding episodes was 6.429 (4.979) months (median: 5.495 months; range: 0.617; 22.686 months).

Weight-adjusted consumption of ADYNOVATE




The mean (SD) weight-adjusted prophylactic dose per infusion as calculated for all subjects on prophylaxis was 51.363 (8.829) IU/kg.

6.2.11.3 Subpopulation Analyses

There was 1 female subject versus 215 male subjects in this study, therefore the statistical analysis of ABR for male subjects is similar that of FAS and the statistical analysis of ABR for the female subject is not meaningful.

The spontaneous ABR subgroup analysis based on the age category is shown above in Table 11. Compared to the overall spontaneous ABR for the twice weekly fixed dose regimen (1.197), the spontaneous ABR (95% CI) was similar (1.259 [0.876 - 1.812]) for subjects ≥ 18 years of age, lower for subjects aged < 6 years (0.656 [0.394 - 1.094]) and for subjects ≥ 6 to < 12 years (0.762 [0.438 - 1.325]), and higher for the ≥ 12 to < 18 year age category (1.768 [1.093 - 2.859]).

(b) (4)



6.2.12 Safety Analyses

6.2.12.3 Deaths

One subject (Subject (b) (6) a 15-year-old Asian male) died during the study of an SAE of cerebral hemorrhage considered unrelated to study treatment.

6.2.12.4 Nonfatal Serious Adverse Events

Fifty-two AEs in 33/216 (15.3%) subjects, including Subject (b) (6), were serious. None of these SAEs were considered related to ADYNOVATE by investigator or sponsor assessment.

6.2.12.5 Adverse Events of Special Interest (AESI)

Development of inhibitory antibodies to FVIII (≥ 0.6 BU) was the primary safety outcome measure for this study. One subject (Subject (b) (6), a 3-year-old Black/African American male, had a single positive FVIII inhibitor result of 0.6 BU in the (b) (4) assay performed at the central laboratory at 24 months (b) (6), 740 days after first ADYNOVATE infusion in Study 261302). This

subject returned on (b) (6) for retest and the inhibitor titer was negative (<0.4 BU).

No other confirmed FVIII neutralizing antibodies development was observed in this study.

6.3 Trial #3: 261204

6.3.1 Objectives

The primary objective was to evaluate the perioperative hemostatic efficacy of ADYNOVATE in male PTPs with severe hemophilia A (FVIII <1%) undergoing major or minor elective or minor emergency surgical, dental or other invasive procedures.

Secondary objectives include:

- To determine intra- and post-operative blood loss, volume of blood, red blood cells, platelets, and other blood products transfused, the occurrence of bleeding episodes and additional need for surgical intervention, and daily and total weight-adjusted consumption of ADYNOVATE per subject
- To determine the safety of ADYNOVATE in subjects undergoing surgery, as assessed by occurrence of AEs and changes in vital signs and clinical laboratory parameters
- To determine Incremental recovery (IR) following the initial bolus infusion prior to surgery

6.3.2 Design Overview

This was a Phase 3, prospective, open-label, single-group, uncontrolled, multicenter study to evaluate the efficacy and safety of ADYNOVATE in subjects undergoing major or minor elective or minor emergency surgical, dental or other invasive procedures.

Subjects were eligible if they were actively participating in or had completed participation in another ADYNOVATE study (pivotal study 261201, pediatric study 261202 or continuation study 261302) or were newly recruited and met the pre-specified entry criteria defined. While subjects transitioning from another study had the option to undergo minor elective or minor emergency surgical, dental or other invasive procedures, newly recruited subjects were required to be in need of a major elective surgical, dental or other invasive procedure.

Major Surgeries

Major surgeries required moderate or deep sedation, general anesthesia, or major conduction blockade for subject comfort. It generally referred to major orthopedic (e.g., joint replacement), major abdominal, intracranial, cardiovascular, spinal and any other surgery which had a significant risk of large

volume blood loss or blood loss into a confined anatomical space. Major surgeries/interventions were expected to require clinical surveillance or hospital treatment >3 days after the surgery/intervention.

Minor Surgeries

Minor surgeries could be safely and comfortably performed on a subject who received local or topical anesthesia, without more than minimal preoperative medication or minimal intraoperative sedation. Minor surgeries/interventions were expected to require clinical surveillance or hospital treatment ≤ 3 days after the surgery/intervention

6.3.3 Population

Inclusion Criteria

For transitioning subjects from another ADYNOVATE study:

1. Subject required minor or major elective, or minor emergency surgical, dental or other invasive procedure
2. Subject and/or legal representative provided signed informed consent.
3. Subject continued to meet eligibility criteria as outlined in the parent ADYNOVATE study.

For newly entering subjects:

1. Subject required an elective major surgical, dental or other invasive procedure.
2. Subject and/or legal representative provided signed informed consent.
3. Subject was 12 to 75 years of age at the time of enrollment.
4. Subject is male with severe hemophilia A (FVIII level <1%) as confirmed by the central lab at screening.
5. Subject was previously treated with FVIII concentrates with ≥ 150 documented EDs.
6. Subject was currently receiving prophylaxis or on-demand therapy with FVIII concentrate.
7. Subject had a Karnofsky performance score of ≥ 60 at screening.

Exclusion Criteria

For transitioning subjects:

1. Subject required major emergency surgery
2. Subject developed thrombotic disease, fibrinolysis or disseminated intravascular coagulation (DIC) during the parent study.
3. Subject had a platelet count $< 100 \times 10^9/L$, as confirmed by the central laboratory at screening.
4. The subject had an IR < 1.5 IU/dL:IU/kg as determined in the parent study, if applicable.

For newly entering subjects:

1. Subject had detectable FVIII inhibitory antibodies (≥ 0.4 Bethesda Units (BU) using the (b) (4) Bethesda assay) at screening

- as determined by the central laboratory or at any time point prior to screening (≥ 0.4 BU using the (b) (4) Bethesda assay or ≥ 0.6 BU using the Bethesda assay).
2. Subject had severe renal impairment (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening.
 3. Subject had severe chronic hepatic dysfunction (eg, ≥ 5 X upper limit of normal alanine aminotransferase (ALT), as confirmed by central laboratory at screening, or a documented INR > 1.5).
 4. Subject required minor emergency or elective surgery.
 5. Subject required major emergency surgery
 6. Subject had a history of ongoing or recent thrombotic disease, fibrinolysis or disseminated intravascular coagulation (DIC).
 7. Subject had a platelet count $< 100 \times 10^9/L$, as confirmed by the central laboratory at screening.
 8. Subject had a known hypersensitivity towards mouse or hamster proteins, polysorbate 80 or to PEG.
 9. Subject was currently using or had recently (< 30 days) used pegylated drugs (other than ADYNOVATE) prior to study participation or was scheduled to use such drugs during trial participation.
 10. Subject was currently participating in another clinical drug (other than ADYNOVATE) or device study or use of another investigational product or device within 30 days prior to study entry.
 11. Subject had a diagnosis of an inherited or acquired hemostatic defect other than hemophilia A.
 12. Subject was currently receiving, or scheduled to receive during the course of the study, an immunomodulating drug (e.g., systemic corticosteroid agent at a dose equivalent to hydrocortisone greater than 10 mg/day, or alpha interferon) other than anti-retroviral chemotherapy.
 13. Subject had a clinically significant medical, psychiatric, or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Within 60 minutes before initiating surgery, subjects received a loading dose of ADYNOVATE to raise the pre-infusion plasma level of FVIII to 80-100 % of normal for major and to 30-60 % of normal for minor procedures.

The dose and frequency of ADYNOVATE administered was individualized based on the subject's PK parameters for major surgeries and the most recent IR value for minor surgeries and the required FVIII target levels. The formula for calculating the required number of units was as follows:

Required units (IU) =
body weight (kg) x desired FVIII rise (IU/dL) x {reciprocal of IR} (IU/kg)/(IU/dL)

6.3.6 Sites and Centers

Subjects were enrolled at 12 sites in 7 countries.

6.3.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint was the GHEA score, which is composed of three individual ratings:

- Assessment of intraoperative hemostatic efficacy of ADYNOVATE performed by the operating surgeon
- Assessment of postoperative hemostatic efficacy of ADYNOVATE performed on postoperative Day 1 (i.e., the day following the day of surgery) by the operating surgeon
- Assessment of perioperative hemostatic efficacy of ADYNOVATE performed by the investigator at discharge or on postoperative Day 14 (whichever is first)

A treatment success was defined as a GHEA rating of excellent or good.

Secondary efficacy endpoints included:

- Intra- and post-operative blood loss at the end of surgery, at postoperative Day 1 and until discharge or Day 14 (whichever is first), as applicable, compared to the estimated volume of expected average and maximum blood loss in a comparable healthy individual as predicted preoperatively by the investigator/surgeon
- Volume of blood, red blood cells, platelets, and other blood products transfused
- Occurrence of bleeding episodes and additional need for surgical intervention
- Daily and total weight-adjusted consumption of ADYNOVATE per subject

Safety endpoints included:

- Incidence of inhibitory antibodies to FVIII
- Development of binding antibodies to FVIII, ADYNOVATE, and PEG
- Development of binding antibodies to CHO proteins
- Occurrence of thrombotic events
- Incidence of severe allergic reactions (e.g. anaphylaxis)
- Other investigative product (IP)-related AEs
- Incidence of clinically significant changes in vital signs and routine laboratory parameters (hematology, clinical chemistry)

6.3.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Determination

The sample size of approximately 50 major and minor surgeries in approximately 40 subjects to evaluate a minimum of 10 major surgical/invasive procedures in at least 5 subjects was determined by the number of subjects requiring major elective and minor emergency or elective surgical, dental or other invasive procedures and was not based on statistical considerations.

Analysis Sets

The full analysis set (FAS) comprised all subjects with at least one available hemostatic assessment. The primary efficacy outcome of GHEA score would be analyzed using FAS.

The per-protocol analysis set (PPAS) comprised all subjects with available:

- 1) intraoperative efficacy assessment performed by the operating surgeon within 60 minutes post-surgery,
- 2) postoperative hemostatic control assessed by the operating surgeon postoperatively at 24 hours and
- 3) perioperative hemostatic control assessed by the investigator during the end-of-study visit

Only subjects who met all study entry criteria and had no major protocol violations that might impact hemostatic efficacy assessments were included in the PPAS.

The safety analysis set (SAS) comprised all subjects who received at least one infusion of ADYNOVATE.

Primary Efficacy Analysis

For the primary efficacy endpoint, point estimates and corresponding two-sided exact (Clopper-Pearson) CIs at the 90% confidence level were calculated for the rate of hemostatic efficacy assessments with excellent/good outcome. No hypothesis testing was planned.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

There were 30 surgical enrollments in 23 unique subjects (7 subjects enrolled more than once, of whom 5 received ADYNOVATE for more than one surgical procedure.)

Of the 30 surgical enrollments, subject (b) (6) failed screening and the remaining 29 enrollments (22 unique subjects) were exposed to ADYNOVATE and included in the SAS.

Three surgical enrollments in two subjects discontinued from the study before the surgery. Overall, the FAS includes 26 surgical enrollments (21 unique subjects). (One subject had two surgical enrollments: one enrollment was cancelled because the subject refused that surgery and another surgical enrollment remained in the study. Therefore, there are 21 unique subjects in the FAS.)

Of the 26 surgical enrollments, 21 were major surgeries comprised of 14 orthopedic procedures and 7 non-orthopedic procedures. There were 5 minor surgeries.

Nine protocol deviations were major: six in the category ‘protocol schedule’, two in the category ‘eligibility’ and one in “procedures not done”. Thus, 12 surgical enrollments (including 10 major and 2 minor) in 11 subjects were included in the PPAS.

The number of subjects and surgeries in each analysis set is provided in Table 14.

Table 14: Analysis Populations

<i>Population</i>	<i>Number of subjects n (%)</i>	<i>Number of surgeries</i>
Enrolled subjects	23	30
SAS	22	29
FAS	21	26
PPAS	11	12

6.3.10.1.1 Demographics

In the SAS, all subjects were male and between 16 and 61 years of age, with a mean (SD) of 34.8 (13.47) years. The majority of subjects were white (27/29 surgical enrollments; 20/22 unique subjects). One subject was Asian and one was Black or African American (one surgical enrollment each).

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All but two unique subjects (three surgical enrollments) had a history of hemophilic arthropathy. The FVIII gene mutation was available for eight unique subjects (nine enrollments): four had an inversion at intron 22, and frame shift, deletion, nonsense and point mutation were reported in one subject each.

Among the 29 surgical enrollments, 23 (79.3%) were reported to have a medical history in the category of infectious disease. Medical history in the musculoskeletal and gastrointestinal categories was reported for the majority of surgical enrollments (21 [72.4%] and 15 [51.7%], respectively).

6.3.10.1.3 Subject Disposition

Three (3/29, 10.3%) surgical enrollments (2 [2/22, 9.1%] unique subjects) discontinued study participation prior to surgery.

Twenty-five surgical enrollments (in 20 unique subjects) completed the protocol following treatment with ADYNOVATE for surgery. One subject (Subject 261204-(b) (6)/261204(b) (6)) withdrew from the study following surgery.

Table 15 summarizes subject disposition.

Table 15: Subject Disposition

<i>Category</i>	<i>Total subjects</i>	<i># of surgeries</i>
Enrolled subjects	23	30
Screen failure	1	1
SAS	22	29
Discontinued before surgery	2	3
Major	17	22
Orthopedic surgeries	12	14
Non-orthopedic surgeries	6	7
Minor	4	5
Discontinued before study completion	1	1
Completed	20	25
Major surgeries	16	20
Minor surgeries	4	5

Source: Adapted from sBLA 125566/325 Module 5.3.5.2: 261204-report-body.pdf, Figure 1, page 51.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

Two of the minor surgeries (one intraoperative and one postoperative for subject (b) (6)) do not have GHEA scores available. The remaining 24 surgeries (21 major and 3 minor) with available GHEA scores in the FAS were rated excellent and therefore considered a treatment success with a 95% CI of (0.858, 1.0).

All surgeries in the PPAS were rated excellent with a 95% CI of (0.735, 1.0).

6.3.11.2 Analyses of Secondary Endpoints

Intra- and Post-operative Blood Loss

Estimates of the volume of actual intraoperative blood loss were available for 14/14 major orthopedic surgeries, 6/7 major non-orthopedic surgeries and 5/5 minor surgeries. The median observed blood loss intraoperatively was 10.0 mL for major orthopedic surgeries, 4.5 mL for non-orthopedic major surgeries and 5.0 mL for minor surgeries. For orthopedic major surgeries, actual blood loss was substantially less than the average volume predicted pre-operatively for the applicable types of procedures by the surgeons/investigators as shown by the median difference from predicted volume of 125.0 mL. For non-orthopedic major surgeries and minor surgeries, intraoperative blood loss was similar to the predicted average volumes.

Transfusion Requirements

No blood transfusions were required intraoperatively; five blood transfusions (packed red blood cells) were administered post-operatively for four surgeries in three unique subjects. Three blood transfusions were administered for three major orthopedic surgeries (in two unique subjects) and two blood transfusions

were administered for a single major non-orthopedic surgery. All transfusions were indicated for low hemoglobin. The mean (\pm SD) volume of transfused blood per surgical enrollment with transfusions was 438.0 (\pm 152.86) mL (range: 293; 600 mL).

Bleeding Episodes

A total of five BEs in five unique subjects were reported in the FAS; three were mild, one was moderate and one was severe. Three BEs required no treatment with FVIII products and the remainder was treated with FVIII products. No additional surgical intervention was required. All BEs were categorized as injury-related; none were categorized as spontaneous or of unknown cause.

6.3.11.3 Subpopulation Analyses

All subjects were male so the subgroup analysis for sex is the same as that of the primary analysis result. The subgroup analyses for age, race, and ethnicity are summarized in Table 16.

Table 16: Subgroup Analysis for Primary Efficacy Analysis
(24 surgeries with GHEA available in FSA)

Category	# of surgeries	90% CI	95% CI
Age			
2 to < 18	1	NA	NA
18 to 75 years	23	0.878, 1.0	0.852, 1.0
Race			
Asian	1	NA	NA
Black or African American	1	NA	NA
White	22	0.873, 1.0	0.846, 1.0
Ethnicity			
Hispanic or Latino	3	0.368, 1.0	0.292, 1.0
Not Hispanic or Latino	21	0.867, 1.0	0.839, 1.0

6.3.12 Safety Analyses

6.3.12.3 Deaths

None of the subjects died during the study.

6.3.12.4 Nonfatal Serious Adverse Events

One moderate and three severe treatment-emergent SAEs occurred, all of which were considered unrelated to ADYNOVATE. The moderate treatment-emergent SAE was device related infection, occurred in Subject 261204-(b) (6) who had major orthopedic surgery. The three severe SAEs include one event of esophageal ulcer and two events of diabetic gastroparesis, which all occurred in Subject 261204-(b) (6). Subject 261204-(b) (6) enrolled twice and received one infusion per enrollment for the PK assessment but did not undergo surgery.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

In this statistical memo, I reviewed the statistical analysis results from three studies: 261303, 261302, and 261204.

Study 261303 was a phase 3, prospective, randomized, open-label, multicenter clinical study. A total of 115 subjects were randomized into two arms. The proportion of subjects who had a zero ABR over the second 6-month study period was (b) (4)

Study 261302 was a phase 3b, prospective, open label, multicenter continuation study of safety and efficacy of ADYNOVATE in the prophylaxis of bleeding. The spontaneous ABR was reported for the twice-weekly prophylaxis (N=186), fixed-dose prophylaxis every 5 days (N=56), and fixed-dose prophylaxis every 7 days (N=15) as 1.197 (95% CI: 0.918, 1.561), (b) (4) respectively.

Study 261204 was a phase 3, multicenter, open label study of efficacy and safety of ADYNOVATE in PTPs with severe hemophilia A undergoing surgical or other invasive procedures. All 24 surgeries (21 major and 3 minor) with available GHEA scores were rated excellent and therefore considered a treatment success (90% CI: 88.3% to 100.0%; 95% CI: 85.8% to 100.0%).

No safety issues were detected in any of the three clinical trials. There were 12 serious adverse events (SAE) in Study 261303, 52 SAEs in Study 261302 and 4 SAEs in study 261204. Among all 68 SAEs, there was only one SAE in Study 261303 was considered related to ADYNOVATE by investigator and sponsor assessment. There was one death occurred during Study 261302, which was considered unrelated to the study treatment.

10.2 Conclusions and Recommendations

This PAS BLA for ADYNOVATE proposes labeling changes in (1) dosing and administration in prophylaxis, (2) clinical studies, and (3) adverse drug reactions. (b) (4)

I defer to the clinical reviewer to determine if the totality of evidence supports the other proposed labeling changes.