## Summary Basis for Regulatory Action

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<thead>
<tr>
<th>Date</th>
<th>November 13, 2015</th>
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</thead>
<tbody>
<tr>
<td>From</td>
<td>Ze Peng, PhD, Committee Chair</td>
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<tr>
<td>BLA #</td>
<td>STN 125566/0</td>
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<tr>
<td>Applicant</td>
<td>Baxalta US Inc.</td>
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<tr>
<td>Date of Submission</td>
<td>November 25, 2014</td>
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<tr>
<td>PDUFA Goal Date</td>
<td>November 25, 2015</td>
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<tr>
<td>Proprietary Name /</td>
<td>ADYNOVATE / Antihemophilic Factor (Recombinant), PEGylated</td>
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<tr>
<td>Established names</td>
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<tr>
<td>Dosage form</td>
<td>Lyophilized powder with nominal potencies: 250 IU, 500 IU, 1000 IU or 2000 IU per vial</td>
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<tr>
<td>Proposed Indication(s)</td>
<td>Indicated in adolescent and adult patients (12 years and older) with congenital hemophilia A (congenital factor VIII deficiency) for:</td>
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<td></td>
<td>• On-demand treatment and control of bleeding episodes</td>
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<td></td>
<td>• Routine prophylaxis to reduce the frequency of bleeding episodes</td>
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<td></td>
<td>ADYNOVATE is not indicated for the treatment of von Willebrand disease.</td>
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<td>Recommended Action:</td>
<td>Approval</td>
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</table>

### Signatory Authorities Action

**Jay S. Epstein, MD**

*Offices Signatory Authority:*

- [ ] I concur with the summary review
- [ ] I concur with the summary review and include a separate review or addendum to add further analysis
- [ ] I do not concur with the summary review and include a separate review or addendum

**Mary Malarkey**

*Office Signatory Authority:*

- [ ] I concur with the summary review
- [ ] I concur with the summary review and include a separate review or addendum to add further analysis
- [ ] I do not concur with the summary review and include a separate review or addendum
1. Introduction

Baxter Healthcare Corporation (now Baxalta US Inc., abbreviated as Baxalta) has submitted an original biologics license application (BLA) to seek U.S. licensure for Antihemophilic Factor (Recombinant), PEGylated. The intended commercial product is a lyophilized powder in a crimp-sealed, stoppered, glass vial, available in nominal dosage strengths of 250, 500, 1000 or 2000 international units (IU) of Factor VIII (FVIII) potency. The product is reconstituted with the provided diluent (sterile Water for Injection, sWFI), for intravenous administration. The proprietary name of the product to be marketed in the U.S. is ADYNOVATE.

ADYNOVATE is indicated for adolescent and adult patients (12 years and older) with hemophilia A (congenital factor VIII deficiency) for: (1) on-demand treatment and control of bleeding episodes, and (2) routine prophylaxis to reduce the frequency of bleeding episodes. ADYNOVATE is not indicated for the treatment of von Willebrand disease.

2. Background

ADYNOVATE is a PEGylated full-length recombinant FVIII (rFVIII) product manufactured by modifying the U.S.-licensed rFVIII product, ADVATE, with a 20-kDa branched polyethylene glycol (PEG) reagent. The product consists of a mixture of rFVIII molecules modified with varying degrees of PEGylation, and contains on average of PEG per mole of rFVIII. The U.S. licensed rFVIII bulk drug substance (BDS), ADVATE, is produced by recombinant DNA technology from Chinese hamster ovary (CHO) cells.

The functional characteristics, in vitro potency in standard clotting assays, and the clinical hemostatic activity of ADYNOVATE are consistent with those of other human FVIII products, and enable the formation of a fibrin clot.

The elimination half-life of ADYNOVATE is 14.3 hours compared to the half-life of the parent molecule ADVATE which is 10.4 hours. ADYNOVATE exhibits an extended terminal half-life
through pegylation of ADVATE, which reduces its binding to low density lipoprotein receptor-related protein (LRP1), the physiological clearance receptor of FVIII. As a result, ADYNOVATE is longer-acting and was developed for intravenous replacement therapy or prophylaxis on a less frequent basis than ADVATE in adult and adolescent patients with hemophilia A. The proposed indications include on-demand treatment and control of bleeding episodes and routine prophylaxis in adolescents and adults.

To support licensure for the above-mentioned proposed indications, the clinical development program for ADYNOVATE included data from a non-randomized open-label 2-arm treatment study in previously treated patients (PTPs) evaluating efficacy, safety and pharmacokinetics (PK) where subjects with severe hemophilia A aged 12 years and above received either a prophylactic regimen of 45 IU/kg twice weekly for at least 50 exposure days (Arm A, n = 121) or an on-demand dosing regimen using individual doses ranging from 10 to 60 IU/kg (Arm B, n = 17) for approximately six months. Among subjects who had been receiving on-demand treatment with a FVIII replacement product at the time of treatment group assignment, the first 17 consecutive subjects were assigned to the on-demand group. The remainder of subjects who had been receiving on-demand replacement therapy, as well as all subjects who had been receiving routine prophylaxis with a FVIII product were assigned to the routine prophylaxis group. Overall, ADYNOVATE was effective in prophylactic and on-demand dosing in adolescent and adult hemophilia A subjects (12 years and older). A safety and efficacy study in pediatric subjects less than 12 years of age is now ongoing; the safety, efficacy, and pharmacokinetic profiles of ADYNOVATE have not been established in these patients.

Although ADYNOVATE is not approved in any country, ADVATE, the starting material in the manufacture of ADYNOVATE has been licensed in the U.S. since July 2003.

This original BLA was reviewed under the PDUFA V program (Standard 12 Month), and the review milestones for this BLA are listed as follows:

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Date</th>
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<tr>
<td>Received</td>
<td>November 25, 2014</td>
</tr>
<tr>
<td>Filing date</td>
<td>January 8, 2015</td>
</tr>
<tr>
<td>Mid-cycle communication</td>
<td>May 7, 2015</td>
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<tr>
<td>Late cycle meeting (external)</td>
<td>August 6, 2015 (cancelled by the applicant)</td>
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<tr>
<td>Advisory Committee</td>
<td>Waived</td>
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<tr>
<td>Action Due</td>
<td>November 25, 2015</td>
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</tbody>
</table>

3. Chemistry, Manufacturing and Controls (CMC)

a) Product Quality

_Description_
ADYNOVATE is a sterile, non-pyrogenic, white to off-white lyophilized powder for reconstitution for intravenous injection. The reconstituted product contains the following excipients and stabilizers: tris (hydroxymethyl) aminomethane (Tris), calcium chloride, mannitol, sodium chloride, trehalose dihydrate, glutathione, histidine, and polysorbate 80. ADYNOVATE is supplied in single-use vials containing nominal potencies/amounts of 250, 500, 1000 or 2000 IU per vial. Each vial is labeled with the actual FVIII activity in IU determined using the one-stage clotting assay, and a reference material calibrated against a World Health Organization (WHO) International Standard for FVIII concentrates.

Summary of Manufacturing Process

ADYNOVATE BDS is manufactured at Baxalta’s facility (Suite (b) (4)). The starting material in the manufacture of ADYNOVATE is the commercial ADVATE bulk manufactured at either Baxalta’s (Suite (b) (4)). After the starting material is with a 20-kDa branched PEG reagent. The PEGylated rFVIII is then purified by (b) (4). The ADYNOVATE drug product (DP) is manufactured at Baxalta’s (b) (4). After the vials are filled and partially stoppered, the product is lyophilized. The vials are fully stoppered after the completion of lyophilization and then capped with a flip-off cap. The vials are shipped under controlled temperature (2 – 8°C) from Baxalta’s (b) (4) facility to Baxalta’s facility at for labeling, secondary packaging, and boxing.

Source material quality and control

ADVATE, the starting material of the manufacture of ADYNOVATE, is produced in CHO cells. Master Cell Bank, Working Cell Bank, and an end-of-production cell bank were characterized for adventitious agent safety, genotypic quality, and phenotypic quality during the licensure of ADVATE. All other source materials used for ADYNOVATE manufacture are either compendial or in-house specified, and do not contain animal- or human-derived materials that could potentially introduce contamination with adventitious agents. All source materials are purchased from the approved suppliers and released against the approved specifications.

Critical process parameters and their control
Critical process parameters (CPPs) for the manufacturing process and their acceptable ranges were initially determined during process development. The acceptance ranges were further verified and adjusted during the optimization of the process steps and production of full-scale GMP lots. Operating parameters for each unit operation in the ADYNOVATE process were examined for criticality prior to the execution of the conformance campaigns. These CPP parameters and their acceptance criteria have been justified.

**Process validation**

The manufacturing process of ADVATE BDS was evaluated during the licensure of ADVATE. For the steps from the ADVATE BDS to ADYNOVATE BDS, the process validation was executed with the production of consecutive conformance batches (i.e., batches Baxalta manufactured one additional batch (i.e., batch using extended process and hold times. Four of these batches were monitored for long-term stability.

For the manufacturing process of ADYNOVATE DP, process validation was conducted through manufacture of: 250 IU lots, 500 IU lots, 1000 IU lots, and 2000 IU lots, covering minimum and maximum lot sizes. Conformance lot information is listed as follows:

(b) (4)

Process and quality controls for conformance batch/lot manufacture complied with prospectively defined acceptance criteria for successful process validation.

**Analytical characterization**

ADYNOVATE is a PEGylated full-length rVIII product. The PEG-rFVIII conjugate is linked via a stable bond to lysine side chain residues (see below) present mainly in the...
ADYNOVATE contains on average \( (b) (4) \) of PEG per mole of rFVIII. Thus, the average molecular mass of ADYNOVATE is approximately \( (b) (4) \) of which the protein moiety constitutes approximately 280 kDa (2,332 amino acids).

Clinical and commercial scale ADYNOVATE DS and DP were characterized for \( (b) (4) \). Data derived from the \( (b) (4) \) batches confirmed the consistency of the site-specific PEGylation predominantly on the \( (b) (4) \).

Furthermore, Baxalta identified that \( (b) (4) \). Additionally, the data derived from these conformance batches indicate similar characteristics of ADYNOVATE and unmodified rFVIII in terms of \( (b) (4) \). These data demonstrate that the functional characteristics and hemostatic activity of ADYNOVATE are consistent with those of human FVIII products, e.g., ADVATE.

**Impurities**

Product- and process-related impurities were identified and characterized in selected batches/lots of DS and DP that were studied in clinical trials. Removal of product- and process-related impurities by the manufacturing process was confirmed in the validation of the commercial
In general, the product- and process-related impurities among the conformance lots are comparable, and the levels of these impurities are well controlled.

Process-related impurities: The test results indicated that the levels of host cell proteins were further reduced in the manufacture of ADYNOVATE in comparison to ADVATE DS. The concentration of Tris was either significantly reduced or below the respective limit of detection of each method. Additionally, upon our request, Baxalta provided data to show that the residual murine IgG from ADVATE is not enriched during the manufacturing process of ADYNOVATE, although ADVATE is. Results also indicate that the majority of the residual murine IgG was—(b) (4)

The maximum concentration of Tris in ADYNOVATE DP is per kg body weight, which results in a safety margin of 11000 fold. Free PEG was detected starting with the step. This impurity was significantly reduced after steps, and well controlled in DP of ADYNOVATE. Because free PEG from the PEGylated protein was observed to occur under stress conditions such as, this impurity is monitored throughout the relevant stability studies. Baxalta confirmed that the free PEG in ADYNOVATE consisted of and using a method.

Product-related impurities: Comparing with ADVATE, ADYNOVATE did not show a significant difference regarding the levels of

Specification for final drug product

The following release specifications are considered adequate to confirm product quality and manufacturing consistency.

<table>
<thead>
<tr>
<th>Product quality attribute</th>
<th>Specification</th>
<th>Test method (Procedure number)</th>
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</thead>
<tbody>
<tr>
<td><strong>Appearance of lyophilized cake</strong></td>
<td>White to off-white friable powder</td>
<td>Visual (NE-11-00052)</td>
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<tr>
<td><strong>Appearance of reconstituted solution</strong></td>
<td>Clear, colorless solution substantially free from foreign particles</td>
<td>(b) (4)</td>
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<tr>
<td><strong>Reconstitution time</strong></td>
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</table>
### Identity

- **FVIII Activity**: 200 – 2500 IU/vial; Report for calculation
- **FVIII Activity (Clotting)**: of the final targeted potency; One-stage clotting assay (NE-13-00032)
- **Specific FVIII activity (Clotting)**: 2700 – 8000 IU/mg; Calculation

### Purity

- **Free FVIII subunits**
- **Free PEG**
- **Total PEG**: Report for calculation
- **Degree of PEGylation**: Calculation
- **Residual moisture**

### Excipients

- **Polysorbate 80**
- **Calcium**
- **Sodium**
- **Mannitol**
- **Trehalose-Dihydrate**
- **Tris**
- **Histidine**
- **Total Glutathione**

### Safety

- **Particulate matter**
Suitable analytical methods have been validated to support quality control testing throughout manufacture, final product release, and stability monitoring. Clarifications were obtained through requests of additional documentation. All identified issues were adequately resolved in the course of the review through requests of supplemental data, or method re-validation. In particular:

- During the validation of Total PEG assay several calculation mistakes were made. Namely, the range of the assay was validated incorrectly because the endogenous PEG present in the matrix used in the validation was not taken into account. The supplemental validation was performed using the matrix without PEG to address this issue. Also, the recoveries of the PEG spikes were calculated incorrectly, which resulted in the reported assay performance being underestimated. The data were recalculated per FDA request.

- In the validation report for PEG Distribution assay several important pieces of information were missing. In particular, the precision and intermediate precision of the assay were not established in regard to the steps. This information was later provided by Baxalta, as the experiments were performed during the time of validation but data were not included in the report. Also, in the validation report the conclusions regarding the robustness of the assay were made in the absence of pre-determined acceptance criteria; however, the information regarding the establishing of robustness was included in the separate analytical characterization report which was submitted per FDA request.

- In the validation report 2012-BAX 855-CLOTTING-RFPQ1 for FVIII Activity (One-stage clotting assay) from 2012, accuracy was validated by measuring the ADYNOVATE spike recovery in several matrices. For all matrices tested, percentages of spike recovery were higher for the spikes of higher potency. Thus, the assay results may be affected by changing the dilution within the established range. The data for robustness validation also demonstrated a dependence of assay results from time the sample spent in the instrument before analysis, with significant upward trend for both matrices (the difference between the first and last sample in the series is These issues were addressed in the additional validation report for the one-stage clotting assay from 2015 and in the modified testing instructions submitted in the amendment to the application.

An acceptable reference standard qualification and maintenance program has been established. Baxalta uses a FVIII in-house potency standard (Lot as a reference standard for testing of PEGylated rFVIII potency based on the following justifications:
No international reference standard is available for testing of PEGylated rFVIII potency at this time.

The potency of the in-house reference standard Lot [redacted] was calibrated against the WHO standard for FVIII potency determination of plasma-derived and recombinant therapeutic concentrates.

The slopes of the response curves (i.e., FVIII activity vs. clotting time) between ADYNOVATE and the reference standard Lot [redacted] are not statistically different.

**Container closure system**

The drug product is filled into clear and colorless glass vials (stoppered with 20 mm gray butyl rubber stoppers), and sealed with aluminum crimp-caps with polypropylene flip-off disks. The diluent is filled into 6 mL glass vials, gray 20 mm chlorobutyl rubber stoppers with [redacted], and 20 mm aluminum flip-off caps. Baxalta conducted container closure integrity testing at the facility employing the [redacted] test method; all acceptance criteria were met.

**Stability studies**

The available stability data indicated no critical trends during the observed long-term storage period. Stability data submitted to this BLA supported the proposed shelf-life of ADYNOVATE of 24 months when stored at 2°C - 8°C. Within this period, the product is allowed to be stored at room temperature (i.e., ≤ 30°C) for up to 1 month not to exceed the expiration date. After reconstitution, the solution must be used within 3 hours under the storage of 2°C - 30°C.

**Evaluation of safety of product regarding adventitious agents**

The safety with regard to non-viral adventitious agents such as bacteria, fungi, and mycoplasma is ensured through the control of source materials, adherence to current good manufacturing practice, in-process control monitoring, validated sterile filtration and aseptic filling processes, and release and stability testing for sterility, endotoxin, and particulate matter.

The cell line for the production of ADVATE, the starting material in the manufacture of ADYNOVATE, has been adapted in a culture medium that does not contain additives of human or animal origin. No animal or human derived raw materials are added in the PEGylation process. Additionally, no raw materials or ingredients of human or animal origin are used in the formulation of ADYNOVATE final product. The potential risk of adventitious viruses or transmissible spongiform encephalopathy agent contamination is minimized in the manufacturing process of ADYNOVATE.

No additional viral clearance steps are included in the manufacture of ADYNOVATE other than those in the manufacture of ADVATE BDS. S/D treatment is a dedicated virus inactivation step in
the manufacture of ADVATE. Immunoaffinity Chromatography steps also contribute to viral removal. Baxalta evaluated these steps in relevant down-scale studies using

These model viruses represent a wide range of size and physico-chemical properties and the results support the effectiveness of the manufacturing process to clear viruses from ADVATE/ADYNOVATE.

b) CBER Lot Release

Under the provision described in Federal Register (FR) 58:38771-38773 and 60 FR 63048-63049 (December 8, 1995), routine lot-by-lot release by CBER is not required for ADYNOVATE because it is a well-characterized recombinant product. Thus, exemption of ADYNOVATE from CBER Lot Release is justified.

The Division of Biological Standards and Quality Control has performed in-support testing of commercial scale ADYNOVATE product lots of 250 IU and 2000 IU nominal potencies. The results confirmed the suitability of critical quality-defining methods for their intended use as lot release specification tests. Test results were deemed consistent with the proposed commercial release specifications.

c) Facilities review/inspection

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

### Manufacturing Facilities Table for ADYNOVATE

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<tr>
<th>Name/Address</th>
<th>FEI Number</th>
<th>DUNS Number</th>
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<td>Team Biologics (b) (4) VAI</td>
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<tr>
<td><strong>Drug Product Manufacturing</strong></td>
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<tr>
<td><strong>Drug Product Labeling</strong></td>
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BAXALTA BLA for ADYNOVATE (STN 125566/0)
The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31 (c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

**Recommendation:**
The manufacturing process for ADYNOVATE is considered validated at the commercial scale and is sufficiently controlled to assure consistent manufacture of commercial product meeting acceptable release specification. The reviewers from the Division of Hematology Research and
Review, the Division of Manufacturing and Product Quality, and the Division of Biological Standards and Quality Control conclude that Baxalta has provided sufficient data and information on chemistry, manufacturing and controls to support the licensure of ADYNOVATE.

4. Non-clinical Pharmacology/Toxicology

a) General Considerations

The safety and effectiveness of ADYNOVATE were characterized in a nonclinical program that included in vivo efficacy testing and induction of thrombogenesis by PEG-FVIII, as well as in vivo pharmacokinetics, local tolerability, and single and repeat-dose toxicity studies in FVIII-deficient (hemophilic) mice, and in FVIII replete (i.e., wild-type) monkeys, rats, and rabbits. A risk assessment of the potential extractable and leachable components present in the PEG-FVIII drug substance, as per the ISO 10993 standards and using clinical experience was also completed.

Previous experience with similar recombinant and plasma-derived FVIII products has demonstrated that the toxicities of exogenously administered FVIII are extensions of its pharmacologic activity, i.e. hypercoagulability of blood, thrombosis, and thromboembolus formation in treated animals and patients. Additional expected nonclinical findings are development of neutralizing and non-neutralizing antibodies directed against the human FVIII protein (i.e., immunogenicity), with the potential to cross-react and neutralize endogenous FVIII in wild-type animals and potential increase in inhibitor antibody titre levels.

b) Nonclinical Findings

Pharmacology
These studies were conducted in a murine model of Hemophilia A (i.e., mice with a naturally occurring mutation/deletion of FVIII function), and in normal, FVIII-replete (i.e., wild-type) monkeys. Hemophilic mice were dosed intravenously with increasing doses of ADYNOVATE, or another approved recombinant human FVIII product, in a cross-over study design. Dosing of 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 times (aPTT) to within normal limits, and the results were comparable to those obtained following dosing with the approved human FVIII product. There were no effects of ADYNOVATE or the other FVIII preparations on the hematology profiles in mice as compared to prior to dosing (i.e., baseline), and no serious adverse effects or evidence of thrombogenicity were reported.

Secondary pharmacology studies with PEG-FVIII in FVIII replete monkeys showed no elevations of ex vivo biomarkers of thrombosis (i.e., thrombin, thrombin-anti-thrombin complex, D-dimer and prothrombin fragments 1+2 formation) at doses up to 12-fold greater than the maximum ADYNOVATE clinical dose. Biomarker results were similar to those achieved in monkeys dosed with the comparator human FVIII product. No abnormal tissue pathology, and
only sporadic evidence of in situ thrombosis with no apparent relationship in the incidence or severity to the FVIII dose level were observed on microscopic examination of lung and other tissues from rats dosed with PEG-FVIII.

In summary, animal studies with PEG-FVIII showed the expected pharmacologic (pro-coagulant) activity in a murine model of Hemophilia A, and the results were similar to those obtained with other approved human FVIII products. There was no evidence of undesirable secondary pharmacologic activity, i.e., thrombogenesis, in FVIII-replete monkeys dosed with PEG-FVIII at dose levels up to 60-fold greater than the equivalent human ADYNOVATE starting dose. These data were used as proof-of-concept to support the rationale for entering ADYNOVATE into clinical trials, and to support the pharmacology section of the ADYNOVATE BLA package insert.

**Pharmacokinetics**

PK studies with ADYNOVATE were conducted concurrently with the pharmacology studies in the Hemophilia A mice, and FVIII activity was measured by both the one-stage clotting and chromogenic assays. With both assays, the PK profiles from hemophilic mice dosed with ADYNOVATE showed dose-dependent increases in all parameters measured, and were comparable to those obtained when the mice were dosed with the approved, human recombinant FVIII comparator. Similar results were obtained in FVIII-replete, wild-type monkeys with ADYNOVATE and an approved, human FVIII comparator product. A series of PK studies in FVIII-replete, wild-type rats and monkeys showed that the PEG-FVIII products tested in the nonclinical safety program were comparable to those used in clinical trials, and that changes in manufacturing during the development program did not affect the critical PK parameters.

**Toxicology**

Overall toxicity studies with ADYNOVATE did not identify any unexpected findings or significant concerns. Monkeys dosed with a single, intravenous injection of PEG-FVIII at doses up to 20-fold greater than the clinical starting dose demonstrated no systemic or tissue pathologies. A repeat dose toxicity study with PEG-FVIII was conducted in rats; animals were dosed every other day for 28 days by bolus intravenous injection with PEG-FVIII doses equal to, and up to 20-fold greater than the clinical starting dose. Although statistically significant differences in some measured parameters of toxicity were reported (e.g., hematology, prothrombin time and aPTT, serum chemistry and urinalysis), the findings were not consistent or dose-related between the PEG-FVIII dose groups, and no corresponding histopathological findings were detected. The findings in the rats following repeat dosing with ADYNOVATE were comparable to those findings in rats receiving equivalent doses of either an approved, recombinant human FVIII product or a human plasma-derived FVIII concentrate (as comparators), suggesting that the safety profile of PEG-FVIII is similar to that of other, approved FVIII products. In a 28-day, repeat dose toxicity study with PEG-FVIII conducted in monkeys, animals were dosed every fifth day for 28 days by bolus intravenous injection with PEG-FVIII doses equal to, and up to 20-fold greater than the clinical starting dose. Although statistically significant differences in some measured parameters of toxicity were reported (e.g., hematology, prothrombin time and aPTT, serum chemistry and urinalysis), the findings were consistent and dose-related between the PEG-FVIII dose groups, and corresponding histopathological findings were detected. Animal findings for toxicity studies
were expected and consistent based on exaggerated pharmacologic effects for recombinant and plasma derived FVIII products. Dermal toxicity and local tolerance studies conducted in rabbits administered the clinical dose of PEG-FVIII revealed acceptable levels of inflammation and edema at the injection site.

Special Toxicology Studies
Nonclinical studies were complete on the 20 kDa PEGylated moiety used in the manufacturing of PEG-FVIII. Complete excretion of the 20 kDa PEG moiety was observed in a nonclinical study investigating the distribution and excretion of radiolabelled PEG-FVIII (labeled PEG reagent) after a single intravenous high dose in rats, representing at least a 30-fold excess over an average single clinical dose. No remarkable toxicities were reported in rats after acute dosing with 20 KDa PEG moiety. Clinical experience with the 20 kDa PEG moiety demonstrates similar results.

There were no animal studies for carcinogenicity, in vivo mutagenicity, fertility, reproductive toxicity or teratogenicity conducted with PEG-FVIII. As PEG-FVIII is a recombinant, human protein, animals receiving repeated doses of the product developed antibodies against FVIII that both accelerated clearance of the protein and in some cases, neutralized its pro-coagulant activity. Therefore, long-term, repeat-dose toxicity studies as well as the standard carcinogenicity bioassay (i.e., 2 years of daily PEG-FVIII dosing in both rats and mice) were not feasible to conduct.

Because PEG-FVIII is a protein, the standard battery of genotoxicity testing as recommended in the International Conference on Harmonization (ICH) S2 guidance documents would not provide information to address potential mutagenicity of the rFVIII, and as per the ICH S6 guidance on biotechnology-derived protein therapeutics, these studies were not required. The lack of carcinogenicity, mutagenicity and chronic toxicity data are addressed in the appropriate section of the package insert.

No nonclinical reproductive or developmental toxicity studies were conducted in support of this submission. Hemophilia A is an X-linked disorder and affects mostly male subjects; therefore, it is highly unlikely that a pregnant or lactating woman would receive PEG-FVIII. ADYNOVATE received a labeling that includes a statement in the package insert that nonclinical reproductive and developmental toxicity studies with ADYNOVATE have not been conducted, and the product should be used in pregnancy only if clearly needed. This labeling is consistent with that included in prescribing information for other approved recombinant human coagulation factors for the treatment of Hemophilia A or B.

Recommendation:
The results from the nonclinical program suggest that the safety profile of ADYNOVATE is sufficient to support its use for the proposed indications in adolescent and adult patients (12 years and older) with hemophilia A of: (1) on-demand treatment and control of bleeding episodes, (2) routine prophylaxis to reduce the frequency of bleeding episodes.

5. Clinical Pharmacology
The clinical pharmacokinetics (PK) of ADYNOVATE have been assessed in two submitted clinical studies (No. 261101 and No. 261201). These studies were designed to evaluate the PK characteristics of ADYNOVATE as well as to compare ADYNOVATE to ADVATE with respect to PK in previously treated patients (PTPs) with severe hemophilia A. PK studies for gender, race and drug-drug interactions have not been conducted.

Study No. 261101 was a Phase 1, prospective, open label, cross-over, dose-escalation study in previously treated patients with severe hemophilia A (FVIII activity < 1%). The study consisted of 2 cohorts. Cohort 1 had 8 evaluable subjects. Cohort 2 had 10 evaluable subjects. Subjects in Cohort 1 received single doses of ADVATE and ADYNOVATE at 30 IU/kg, and subjects in Cohort 2 received single doses of ADVATE and ADYNOVATE at 60 IU/kg. Blood samples for the determination of FVIII plasma activity were taken before infusion and for ADVATE up to 48 hours after the end of the infusion, and for ADYNOVATE up to 7 days post infusion. Blood samples were analyzed for FVIII activity using both the one-stage clotting assay (OS) and the two-stage chromogenic substrate assay (CA). PK data analysis was performed using non-compartmental analysis.

Based on the one-stage clotting assay a comparison of the relevant PK parameters showed the following results for Cohort 1 (Mean ± SD). Terminal plasma half-life = 13.6 ± 2.8 h (ADYNOVATE) and 9.90 ± 1.7 h (ADVATE). Systemic clearance = 0.0215 ± 0.0072 dL/kg/h (ADYNOVATE) and 0.0377 ± 0.0154 dL/kg/h (ADVATE). Incremental in-vivo recovery = 2.73 ± 0.59 IU/dL per IU/kg (ADYNOVATE) and 2.58 ± 0.66 IU/dL per IU/kg (ADVATE). Comparable PK results were obtained in Cohort 2.

The PK parameters assessed using the CA were similar to those obtained from the OS assay. Differences in PK parameter estimates between the two assays were less than 20%. In summary, the PK analyses indicated that the mean terminal plasma half-life of ADYNOVATE is prolonged by approximately 1.4- to 1.5-fold in comparison to ADVATE and the mean clearance decreased by approximately 40%.

Study No. 261201 was a Phase 2/3, multi-center, open label study of efficacy, safety, and pharmacokinetics of PEGylated recombinant factor FVIII. ADYNOVATE was administered for prophylaxis and treatment of bleeding in PTPs with severe hemophilia A (FVIII activity < 1%) with an age range of 12 to 65 years.

The initial PK assessment was performed with ADVATE (PK 1) followed by a PK assessment with ADYNOVATE (PK-2). To evaluate the impact of long-term exposure of ADYNOVATE, a PK assessment was repeated after 22 subjects had completed twice weekly prophylactic treatment for several months (PK3). A dose of 45 IU/kg, both for ADVATE and for ADYNOVATE, was used for PK determination.

Blood samples for the 3 PK evaluations (PK1, PK2, and PK3) were taken at pre-dose, and up to 56 hours after dosing. For ADYNOVATE two blood samples at 72 and 96 hours were added. The blood samples were analyzed for FVIII activity using both OS and CA assays. PK data analysis was performed using non-compartmental analysis.
Based on the OS assay the PK analysis showed the following results for PK2 and PK1 (Mean ± SD). Terminal plasma half-life = 14.3 ± 3.8 h (ADYNOVATE) and 10.4 ± 2.2 h (ADVATE). Systemic clearance = 0.0276 ± 0.02 dL/kg/h (ADYNOVATE) and 0.0455 ± 0.022 dL/kg/h (ADVATE). Incremental in vivo recovery = 2.49 ± 0.69 IU/dL per IU/kg (ADYNOVATE) and 2.37 ± 0.54 IU/dL per IU/kg (ADVATE). Similar results were observed based on the CA. The group mean PK parameters estimated after repeated dosing with ADYNOVATE (PK3) were consistent with the PK parameter estimates after a single dose, even including one outlier adolescent subject (No. 122001) who had a fall in estimated clearance of ADYNOVATE over the course of the trial.

Among adolescents aged 12 to <17 years of age (n = 7 excluding the outlier noted above), the estimated mean [± SD] clearance of ADYNOVATE was 2.73 [0.93] mL/(kg*hr), which was similar to the estimated mean clearance in adults age 18 to 58 years of 2.27 [0.84] mL/(kg*hr) (n = 18). A similar but slightly shorter estimated mean terminal half-life (13.43 [4.05] hr) and lower estimated mean IVR (2.12 [0.60] IU/dL per IU/kg) were observed among adolescents as compared to adults. These minor differences in group mean PK parameters would not be expected to impact dosing recommendations.

In summary, the PK analyses demonstrated that the mean terminal half-life of ADYNOVATE was prolonged by approximately 1.4- to 1.5-fold in comparison to ADVATE. This confirms the results of the Phase 1 clinical study (Report No. 261101). Estimated PK parameters were similar among adults and adolescents.

**Recommendation:**
In general, the PK results of the clinical Phase 1 study and Phase 2/3 study are acceptable from a Clinical Pharmacology perspective. The PK parameter differences between OS and CA assays were less than 20% and appear not to be of clinical significance.

6. **Clinical/Statistical**

**a) Clinical program**

**Summary of Clinical Studies**

The completed, in-progress, and planned post-marketing clinical trials are summarized in the Tables below adapted from BLA 125566/0 Clinical Overview. (BAX 855 = ADYNOVATE)
Table 1. Listing of Studies in the BAX 855 Clinical Development Program

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Short Study Title and Description</th>
<th>Study Status Report (if available)</th>
<th>Sample Size*</th>
<th>Main Criteria for Inclusion</th>
<th>Dose Range and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>261101</td>
<td>BAX 855 Dose-escalation Safety</td>
<td>Complete</td>
<td>19</td>
<td>PTP[-], 10 to 65 years, FVIII -1%</td>
<td>Two sequential dose cohorts: Cohort 1: Single administration of 30 IU/kg BW of ADVATE followed by administration of the same dose of BAX 855 after a wash-out period of 90 days. Cohort 2: Single administration of 60 IU/kg BW of ADVATE followed by administration of the same dose of BAX 855 after a wash-out period of 90 days. Acute bleeding episodes: treated with ADVATE.</td>
</tr>
<tr>
<td>261201</td>
<td>BAX 855 Pivotal Phase 3, multicenter, open-label, 2-arm study to evaluate efficacy, safety, and PK parameters of BAX 855 and BAX 855 at a clinical dose of 30 IU/kg BW.</td>
<td>Complete</td>
<td>138</td>
<td>PTP[-], 12 to 65 years, FVIII -1%</td>
<td>Prophylaxis: 45 IU/kg BW twice weekly for at least 50 EDs or 6 months, whichever occurs last. On-demand: 10 - 60 IU/kg BW for an approximate duration of 6 months. Acute bleeding episodes: treated with BAX 855 and ADVATE and BAX 855 at prophylactic dose level.</td>
</tr>
<tr>
<td>261202</td>
<td>BAX 855 Pivotal Phase 3, multicenter, open-label, 2-arm study to evaluate efficacy, safety, and immunogenicity of BAX 855</td>
<td>Ongoing</td>
<td>60</td>
<td>PTP[-], 60 IU/kg BW over a period of 6 months, or at least 50 EDs. Acute bleeding episodes: treated with BAX 855 and ADVATE and BAX 855 at prophylactic dose level.</td>
<td></td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Short Study Title and Description</th>
<th>Study Status Report (if available)</th>
<th>Sample Size*</th>
<th>Main Criteria for Inclusion</th>
<th>Dose Range and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>261204</td>
<td>BAX 855 Surgery Phase 3, multicenter, open-label, 2-arm study to evaluate efficacy and safety of BAX 855 in surgical or other invasive procedures</td>
<td>Ongoing</td>
<td></td>
<td>PTP[-], 2 to 75 years, FVIII -1%</td>
<td>Prophylaxis: dose tailored to achieve FVIII target levels of 80-100% of normal for major and 30-60% of normal for minor surgeries</td>
</tr>
<tr>
<td>261202</td>
<td>BAX 855 Continuation Phase 3b, prospective, open-label, multicenter, 2-arm study to evaluate efficacy and safety of BAX 855 in the prophylaxis of bleeding</td>
<td>Ongoing</td>
<td>350</td>
<td>PTP[-] who completed either BAX 855 study or BAX 855 native ≤2 years, FVIII -1%</td>
<td>Prophylaxis; dose and frequency based on previous treatment regimen or PK guided to maintain FVIII trough levels of at least 1%, subject exposure for a minimum of 100 EDs as assessed at all BAX 855 studies.</td>
</tr>
<tr>
<td>261203</td>
<td>BAX 855 PUP</td>
<td>Planned</td>
<td>110 (100 evaluable)</td>
<td>PTP[-] who completed another BAX 855 study or BAX 855 native ≤2 years, FVIII -1%</td>
<td>Prophylaxis; 30-35 to 45-60 IU/kg once or twice weekly</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Short Study Title and Description</th>
<th>Study Status Report (if available)</th>
<th>Sample Size*</th>
<th>Main Criteria for Inclusion</th>
<th>Dose Range and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>261303</td>
<td>BAX 855 PK guided Prophylaxis Phase 3, prospective, randomized, open-label, 2-arm clinical study to evaluate efficacy and safety of BAX 855 treatment regimen targeting two different FVIII trough levels</td>
<td>Planned</td>
<td>116 to have 96 evaluable patients (48 per treatment arm)</td>
<td>PTP[-], 20 to 80 years, FVIII -1%</td>
<td>BAX 855 dose will be PK guided to maintain FVIII trough levels 1 - 3% or approx. 10% (8 - 12%) FVIII trough level 1 - 3% at least twice weekly FVIII trough level approx. 10% (8% - 12%) every other day</td>
</tr>
</tbody>
</table>

* Actual sample size for completed studies; planned sample size for ongoing and projected studies.

1 Previously-treated patient (PTP): subject has hemophilia A and has been treated with FVIII product previously.

2 An exposure day (ED) is defined as any calendar day on which at least one infusion of BAX 855 was administered.

Abbreviations: BW = body weight; CSR = clinical study report; ED = exposure day; FVIII = factor VIII; HROQL = health-related quality of life; IU = International Unit; PK = pharmacokinetics; PTP = previously treated patient; PUP = previously untreated patient.

[Source: BLA 125566/0 Clinical Overview]
The safety and efficacy of ADYNOVATE was evaluated in a total of 169 individual PTPs with severe hemophilia A (factor VIII less than 1% of normal), who received at least one dose of ADYNOVATE in two multi-center, prospective, open label clinical studies and 3 ongoing clinical studies. Study subjects consisted of adult (n= 143 with ≥ 150 prior EDs) and pediatric PTPs [(< 6 years of age with ≥ 50 prior EDs (n= 3), ≥ 6 years of age with ≥ 150 prior EDs (n= 23)]. Twelve subjects (7.1%) discontinued the studies prematurely secondary to reasons such as withdrawn consent, adverse events (AEs: arthralgia, trauma-related muscle hemorrhage, humerus fracture and hepatitis C reactivation), and non-compliance unrelated to any adverse events.

A long-term continuation study of the safety and efficacy of ADYNOVATE, a planned randomized trial in PTPs targeting two different trough levels during routine prophylaxis, an ongoing safety and efficacy in surgery trial in pediatric and adult PTP subjects, an ongoing PK, safety, efficacy, and immunogenicity trial in pediatric PTP subjects < 12 years of age, and a planned pediatric PUP study were formalized as postmarketing requirements/commitments and will include ongoing monitoring for inhibitor development, as well as non-inhibitor binding antibodies directed against the product, FVIII, and PEG.

b) Efficacy Analysis

Routine prophylaxis to reduce the frequency of bleeding episodes

Routine prophylaxis with twice weekly administration of 45± 5 IU/kg ADYNOVATE was demonstrated to be effective for reducing the frequency of bleeding episodes in hemophilia A subjects in pivotal trial 261201.

Study 261201 was a phase 2/3, multicenter, open-label, non-randomized two-arm study conducted at 72 multinational sites. The full analysis set consisted of total of 138 subjects assigned to either on-demand therapy with ADYNOVATE (n = 17) or twice-weekly routine prophylaxis (n = 121). Among subjects who had been receiving on-demand treatment with a FVIII replacement product at the time of treatment group assignment, the first 17 consecutive subjects were assigned to the on-demand group. The remainder of subjects who had been receiving on-demand replacement therapy, as well as all subjects who had been receiving routine prophylaxis with a FVIII product were assigned to the routine prophylaxis group. One subject was assigned to routine prophylaxis with ADYNOVATE but received only ADVATE instead of ADYNOVATE and is not included in the safety analysis set (SAS, which herein is also termed the treated population analysis set).

The protocol called for routine prophylaxis subjects to receive ADYNOVATE 45 ± 5 IU/kg twice weekly for 50 exposure days or 6 months ± 2 weeks, whichever occurred later. Subjects receiving routine prophylaxis were dosed at a median dose of 43.6 IU/kg twice weekly (range 41.3 – 46.9 IU/kg) for an actual mean [SD] duration of 5.9 [1.1] months). These subjects averaged a median inter-dose interval of 3.56 days (range 3.52 to 3.68 days) while on prophylaxis during the efficacy period. The on-demand arm subjects were dosed with ADYNOVATE 10 to 60 ± 5 IU/kg for bleeding episodes until the bleeding episode/threat was resolved over a mean [SD] of 6.3 [0.4] months. Demographic 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. This difference was determined to be insufficient to account for the observed difference in annualized bleeding rate (ABR) between the two treatment arms. Of the 121 subjects receiving prophylactic treatments, 21 were previously managed on an on-demand regimen prior to the study. All 17 subjects in the on-demand treatment arm had never received prophylaxis. There were no entry criteria for the number of bleeding episodes for subjects in the on-demand arm. The historical ABR in patients with severe hemophilia A typically ranges between 20 to 50 or more bleeding episodes per year.

A total of 109 subjects in the routine prophylaxis arm and all 17 subjects in the on-demand arm completed the trial. Twelve subjects in the prophylaxis arm (prophylaxis alone and prophylaxis and PK sub-groups) discontinued the trial prematurely: four because of protocol violations, four because of AEs, one for surgery, one for screening failure, and two withdrew consent. One subject who withdrew consent was subsequently diagnosed with a neuroendocrine tumor; another did not resume trial participation after it was interrupted for surgery.

The mean unadjusted ABR in the treated population analysis set (identical to the safety analysis set) who received ADYNOVATE in pivotal trial 261201 was 4.7 in the prophylaxis arm compared to a rate of 40.8 in the on-demand arm (See Table 4 below). Similar results were obtained in the per-protocol analysis set, in which the mean [SD] ABR was 3.7 [4.7] in the prophylaxis arm compared to a rate of 40.8 [16.3] in the on-demand arm. In both the treated population and the per-protocol analyses, using ABR estimates from a negative binomial regression model, there was a statistically significant reduction of 90% in the observed ABR in the routine prophylaxis arm compared to the rate in the on-demand treatment arm (p < 0.0001). There were minor differences in the baseline characteristics of the population in the two arms, most notably that a greater percentage of subjects in the routine prophylaxis arm than in the on-demand arm had no target joints for bleeding at baseline. However the results of both stratified and covariate analyses by target joint status and age were consistent with a substantial reduction in ABR with routine prophylaxis as compared to on-demand treatment. Thus, despite these differences in baseline characteristics, the difference in the bleeding rates during on-demand vs. routine prophylaxis with ADYNOVATE is meaningful.

**Table 4: Annualized Bleed Rate by Treatment for ≥ 12 years of age (Treated Population)**

<table>
<thead>
<tr>
<th>Bleeding Episode Etiology</th>
<th>On-Demand Treatment</th>
<th>Routine Prophylaxis Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Overall</td>
<td>41.5</td>
<td>40.8 (16.3)</td>
</tr>
<tr>
<td>Joint</td>
<td>38.1</td>
<td>34.7 (15.1)</td>
</tr>
<tr>
<td>Non-Joint</td>
<td>3.7</td>
<td>6.1 (6.7)</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>21.6</td>
<td>26.0 (19.6)</td>
</tr>
<tr>
<td>Traumatic</td>
<td>9.3</td>
<td>14.9 (15.3)</td>
</tr>
</tbody>
</table>

[Source: Adapted from Applicant’s Table 23, Clinical Study Report for Trial 261201]
In the subgroups of subjects aged 12 to < 18 years, among 23 routine prophylaxis subjects the mean ABR estimate from the negative binomial regression model was 5.0 (95% CI: 3.2 – 7.7), whereas among 2 on-demand subjects the mean ABR was 39.9 (95% CI: 11.5 – 138.8). Among adults age 18 to 65 years, the estimated mean ABR was 4.1 (95% CI: 3.1 – 5.5), whereas among 15 on-demand subjects the estimated mean ABR was 43.9 (95% CI: 23.9 – 80.8).

When the mean ABR of the subset of subjects in the routine prophylaxis arm who were treated on-demand with FVIII before the trial (n = 21) was compared to that observed in the on-demand arm (all of whom had been on on-demand therapy with FVIII before the trial), a substantial reduction in ABR was noted for the routine prophylaxis subgroup (mean [SD] ABR of 5.7 [13.2] vs. 40.8 [16.3] in the on-demand arm).

Analysis of estimated mean ABR by race using the negative binomial regression model yielded a lower 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.

Race subgroup analyses indicated that ADYNOVATE was effective for routine prophylaxis in whites and Asians. The medical reviewer concluded that ADYNOVATE was 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.

Treatment and control of bleeding episodes

A total of 591 bleeds were treated in 81 subjects during the efficacy period in the pivotal trial with 361 bleeds recorded for on-demand subjects and 230 bleeds for subjects in the prophylaxis arm. Four hundred fifty-five joint bleeds and 136 non-joint bleeds were reported. Eighty-five percent of the total bleeds required one infusion, 11% required 2 infusions and 4% required 3 or more infusions (table 5). The percentage of all bleeds, joint bleeds, and non-joint bleeds treated with one or two infusions was 96.3%, 96.7%, and 94.8% respectively. Of the 120 subjects on prophylaxis, 38% experienced no bleeds. All subjects in the on-demand arm experienced bleeds.

For each bleeding episode, subjects were asked to rate the efficacy of ADYNOVATE 24 hours after initial administration on a 4-point scale from excellent to no response. Ninety-five percent of treatments for bleeds were rated as excellent or good, 3% as fair and 2% as no response or not rated (See Table 5). The lower bound of the 95% confidence interval for the proportion of treatments for bleeds rated excellent or good was 0.91, which was well above the minimum hypothesis test threshold value of 0.70. Consequently, the pre-specified success criterion of this secondary efficacy endpoint for on-demand treatment of bleeding episodes was met.

Table 5: (BAX 855 = ADYNOVATE)
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 aged 18 to 65 years. The point estimates for proportion of bleeding episodes with ADYNOVATE 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 ADYNOVATE 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

The medical reviewer concluded that ADYNOVATE was effective in adults and adolescents for on-demand treatment and control of bleeding episodes.

**Statistical Summary**

Study 261201 was a phase 2/3, multicenter, open-label, non-randomized two-arm study. A total of 159 subjects were screened for enrollment in the study, of whom 137 subjects (treated population analysis set, identical to the SAS) were treated with ADYNOVATE during the treatment period (120 subjects in the prophylactic group; 17 subjects in the on-demand group). Based on a pre-specified generalized linear mixed model analysis, the ratio of the mean ABR for the prophylaxis group versus the on-demand group is 0.1 (95% CI: 0.06, 0.19). The estimated
success rate (excellent or good rating) for the treatment of bleeding episodes expressed as a proportion is 0.96 (95% CI: 0.91, 0.98). The pre-specified study efficacy success criteria for both indications were met.

The statistical results support the claim for use of ADYNOVATE in the treatment of Hemophilia A patients for routine prophylaxis to reduce the frequency of bleeding episodes, and for on-demand treatment and control of bleeding episodes.

c) Pediatric Studies and PREA requirements

The safety, efficacy, and pharmacokinetic profiles of ADYNOVATE have not been established in pediatric patients less than 12 years of age. The safety, efficacy, and pharmacokinetic profiles were similar between adolescent and adult patients in the pivotal study despite pharmacokinetic parameter differences consisting of a greater clearance and somewhat shorter terminal half-life and lower in vivo recovery among adolescents. A pediatric pharmacokinetic, safety, and efficacy study is ongoing with a planned enrollment of 60 subjects (28 for PK) <12 years of age. The safety profile in subjects 12 years and older is acceptable and no safety issues were identified.

d) Bioresearch Monitoring

In consultation with the medical reviewer, one foreign and two domestic clinical investigator study sites participating in the pivotal trial were selected for Bioresearch Monitoring inspections by the Division of Inspections and Surveillance. Inspection outcomes did not reveal significant problems that impacted clinical data submitted to BLA 125566/0.

Conclusion
ADYNOVATE is effective in patients 12 years of age and older for on-demand treatment and control of bleeding episodes and for routine prophylaxis.

7. Safety

Exposure

In addition to the 137 subjects included in the SAS for completed pivotal trial 261201 and 17 additional individual subjects from PK trial 261101 (not also enrolled in trial 261201), the ISS submitted 27 March 2015 also 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.

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

The age breakdown for the 169 ISS subjects was as follows:
### Age Range and Number of Subjects

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 years</td>
<td>3</td>
</tr>
<tr>
<td>6 to &lt; 12 years</td>
<td>1</td>
</tr>
<tr>
<td>12 to &lt; 18 years</td>
<td>25</td>
</tr>
<tr>
<td>≥ 18 years</td>
<td>140</td>
</tr>
</tbody>
</table>

### Safety Analysis

Safety of study subjects was assessed in terms of occurrence of AEs and adverse reactions (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). AEs were analyzed based on the principle of treatment emergence. 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 ARs including severity, seriousness, and relatedness. A DSMB monitored the study.

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

### Deaths

One subject died of neuroendocrine carcinoma approximately three weeks after the 22nd exposure day to ADYNOVATE. The investigator, applicant, and clinical reviewer considered the death unrelated to ADYNOVATE.

### Adverse Events

Across all trials, there were 96/169 (57%) subjects who reported at least 1 AE totaling 300 AEs. In trial 261201 there were five SAEs reported, none of which were judged related to ADYNOVATE. Across all completed and ongoing studies, as of the cutoff date for the March 2015 submission of the ISS, a total of sixteen serious AEs had been reported for 11 subjects; all were unlikely related to ADYNOVATE based on a detailed review of each subject’s case report. Two male subjects in the ongoing continuation trial were hospitalized for acute pancreatitis SAEs. In one severe pancreatitis case, the most likely cause appeared to be concomitant medications for HIV infection. In the other moderate severity case, no cause for acute pancreatitis was identified. 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.
Table 6 below lists the ARs reported during ADYNOVATE clinical studies.

**Table 6:**

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>MedDRA Preferred Term</th>
<th>Number of Subjects (N=169)</th>
<th>Percent per Infusion (N = 13579)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Diarrhea</td>
<td>1 (0.6%)</td>
<td>0.01%</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>2 (1.2%)</td>
<td>0.01%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Headache</td>
<td>5 (3.0%)</td>
<td>0.06%</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Flushing</td>
<td>1 (0.6%)</td>
<td>0.01%</td>
</tr>
</tbody>
</table>

[Source: Integrated Summary of Safety (ISS)]

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 re-challenge.

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

In trial 261201 (and among all 5 completed and ongoing trials) there were a total of four subjects who discontinued treatment with ADVATE prematurely due to AEs; of these, three were considered unrelated and one (treatment-emergent aminotransferase elevation to > 10x the upper limit of normal attributed to hepatitis C reactivation in a patient who was HCV antibody positive at baseline) was considered unlikely related to ADYNOVATE.

**Factor VIII Inhibitors and antibodies**

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

None of the 169 individual subjects included in the March 2015 safety update who received at least one infusion of ADYNOVATE developed neutralizing antibodies to factor VIII and no events of hypersensitivity were reported. There were a total of 120 subjects in pivotal trial 261201 who had at least 50 exposure days (EDs) to ADYNOVATE. The upper bound of the 95% CI for the point estimate of zero inhibitors to FVIII in the pivotal trial 261201 was 3.8%, which is below the 6.8% upper limit which historically has been used by FDA to evaluate the inhibitor rate in PTP trials. Similarly, no patterns of abnormal vital signs or physical examination findings were noted.
Of the 169 subjects in the SAS set, 13 subjects had pre-existing antibodies to factor VIII, PEG-factor VIII or PEG prior to the first exposure to ADYNOVATE. Of these 13 subjects, two subjects had antibodies that persisted throughout the monitoring period. Eight subjects developed antibodies following exposure to ADYNOVATE. In these eight subjects the antibody response was transient and not associated with any recognized pattern of AEs.

No events of hypersensitivity were reported. No patterns of abnormal vital signs or physical examination findings were noted.

Pharmacovigilance

No postmarketing surveillance data were submitted for review because as of November, 2015, ADYNOVATE had not been approved in any country. The available data from clinical trials submitted by Baxalta in support of this BLA permitted an evaluation of potential safety concerns for ADYNOVATE. The safety assessments are as described in the Section 7 in this document. In conclusion, there were no AEs considered allergic/hypersensitivity reactions, none of the subjects developed inhibitory antibodies to FVIII, and no persistent treatment-emergent antibodies to FVIII, PEG FVIII, or PEG were observed in any of the studies. Although these findings are reassuring, the limitations of the clinical safety database with regard to development of FVIII inhibitors, such as absence of larger completed longer-term studies, and absence of data in young children, must be considered when interpreting these results.

A total of 16 SAEs in 11 subjects were observed, none of which were considered related to ADYNOVATE as assessed by the investigator, Baxalta, or FDA. The data submitted in support of this BLA do not identify safety issues in the use of ADYNOVATE for the treatment of bleeding episodes, including for long-term use in adolescent and adult PTPs with severe hemophilia A. Any potential safety issues were adequately addressed by Baxalta in their risk management plan.

8. Advisory Committee Meeting

The Division of Hematology Research and Review and the Division of Hematology Clinical Review in the Office of Blood Research and Review (OBRR) reviewed information from this application and determined that referral to the Blood Products Advisory Committee (BPAC) prior to licensure was not needed for the following reasons (FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE]):

- Although the product is a new molecular entity as there is no previously approved PEGylated rFVIII, the product does not represent new technology as there is ample precedent in FDA for the approval of branched PEG protein therapeutics (Roche’s PEGASYS®, UCB’s CIMZIA®, and Pfizer’s MACUGEN®). As such, OBRR does not need external scientific advice on safety issues that might be associated with a branched PEGylated product. Efficacy of the construct has been clearly demonstrated in clinical
trials and there were no ARs that would preclude approval. Inhibitor development was not seen.

- The mechanism of action of FVIII and its function in blood coagulation are well studied and understood. Upon activation by thrombin, FVIIIa acts as a cofactor for activated Factor IX triggering a chain of biochemical reactions – activation of Factor X, which converts prothrombin into thrombin, and subsequent interaction of thrombin with fibrinogen results in the formation of a fibrin clot that stops bleeding. When administered into a patient with hemophilia A, FVIII products temporarily replace the missing endogenous FVIII.

- ADYNOVATE is a full-length human FVIII. The functional characteristics, in vitro potency in standard clotting assays, and clinical hemostatic activity of ADYNOVATE are consistent with those of other human recombinant, as well as plasma derived FVIII products and enable the formation of a fibrin clot via the intrinsic coagulation pathway.

- ADYNOVATE is manufactured from U.S.-licensed ADVATE DS, whose manufacture includes a dedicated solvent-detergent viral inactivation step, and no human or animal derived materials are used in the manufacture of ADVATE DS, or in the PEGylation process and formulation of ADYNOVATE. Thus product safety with regard to adventitious viruses is assured.

- The proposed indication for ADYNOVATE is similar to that of other U.S. licensed recombinant FVIII products for patients with hemophilia A with the exception that the indication does not include pediatric patients under age 12 years or perioperative management.

- The design of the clinical studies to evaluate the safety and efficacy of ADYNOVATE was adequate, was consistent with those of other approved rFVIII products, and the efficacy and safety results of the studies did not raise any concerns. The studies are considered adequate and well-controlled, and a statistically significant and clinically meaningful reduction in the ABR was observed during routine prophylaxis with ADYNOVATE compared to during on-demand therapy with ADYNOVATE. The size of the safety database for ADYNOVATE (169 subjects) was considered adequate. A long-term continuation study of the safety and efficacy of ADYNOVATE will also be formalized as a post marketing commitment and will include ongoing monitoring for inhibitor development and for non-neutralizing antibodies directed against the product.

- Review of information submitted in the BLA for ADYNOVATE did not raise any controversial issues or pose unanswered scientific questions which would have benefited from Advisory Committee discussion and recommendations.

9. Other Relevant Regulatory Issues
The notable issues raised in the course of the review are described in the respective sections of this document, and they have been satisfactorily resolved through information requests and teleconferences. There were no other relevant regulatory issues.

10. Labeling

a) Proprietary Name

The proposed proprietary name for the product, ADYNOVATE, was reviewed by the Advertising and Promotional Labeling Branch (APLB) and was recommended to be acceptable on May 13, 2015. Other proposed proprietary names submitted previously by Baxalta were recommended to be unacceptable including [redacted], ADVATE PRO, and ADVALTIS. ADYNOVATE was found acceptable as the proprietary name for the product by CBER on May 22, 2015.

b) Conclusions of APLB and Committee Review of Draft Package Insert and Other Labeling

The product labeling (i.e., prescribing information, patient package insert, and instructions for use) were reviewed, commented, and/or revised by the appropriate discipline reviewers before APLB conducted its review from a promotional and comprehension perspective. CBER comments and recommendations regarding the product labeling and carton/vial labels were initially conveyed to Baxalta on August 6, 2015, and discussed throughout the months of August to November 2015.

Final versions of the product labeling (FPI) and labels, submitted to the BLA on November 10, 2015 (Package Insert) and September 24, 2015 (carton and container labels), were considered acceptable. A copy of FPI is attached.

11. Recommendation/Risk Benefit Assessment

a) Recommended Regulatory Action

The CBER review committee recommends approval of this BLA. The manufacturing process for ADYNOVATE, Antihemophilic Factor (Recombinant), PEGylated, is considered validated and adequately controlled. Efficacy and safety clinical data for ADYNOVATE support a favorable benefit/risk determination in adolescent and adult patients (12 years and older) with congenital hemophilia A (congenital factor VIII deficiency) for: (1) on-demand treatment and control of bleeding episodes and (2) routine prophylaxis to reduce the frequency of bleeding episodes. Baxalta has agreed to implement post-marketing commitment (PMC) studies in adults and PREA post-marketing requirement (PMR) studies in pediatric subjects to further evaluate efficacy and safety. These include the ongoing pediatric and extension studies as well as a planned randomized PK target trough comparison study. All required milestone target dates for protocol submission, study completion, and final study report submission have been provided by Baxalta.
b) Benefit/Risk Assessment

The benefits of ADYNOVATE for the proposed indications are considered to outweigh the risks. Effective hemostasis in treatment and control of bleeding episodes and routine prophylaxis was demonstrated in adolescents and adult subjects with severe hemophilia A. Efficacy for these two indications appears comparable to that of licensed recombinant and plasma-derived Antihemophilic Factor (Human) products. The formation of FVIII inhibitors was not observed during the pivotal study. Binding FVIII antibodies that were non-neutralizing were present in 13 subjects (N=169) at screening prior to dosing. Treatment-emergent binding FVIII antibodies were observed in eight subjects and were transient in each case. None of the 21 subjects who demonstrated binding antibodies at any time point showed allergic symptoms or decreased therapeutic effect. One of the subjects had a lower than average half-life at PK assessments 1 and 2 which normalized at PK assessment 3. A risk assessment analysis was performed on subjects with binding antibodies and demonstrated no clinically significant AEs, lack of therapeutic effect, or lasting alterations in pharmacokinetics.

Although ADYNOVATE has a somewhat longer half-life (1.4-1.5x) compared to non-fusion protein marketed rFVIII products, the extent of the possible practical advantage of this product over available therapies has yet to be determined, given that some of the currently licensed recombinant FVIII products, including ADVATE, can also be dosed twice weekly for prophylaxis. The ADYNOVATE pivotal study did show, however, that 93% of the study subjects receiving prophylactic therapy reduced their pre-study dosing frequency by 30% which was equivalent to one less prophylactic infusion per week (i.e. to twice weekly prophylaxis) and this may be of benefit to some patients if this finding proves to be generalizable to the practice setting.

c) Recommendation for Postmarketing Risk Management Activities

Pediatric Requirements

The safety, efficacy, and pharmacokinetic profile of ADYNOVATE have not been established in pediatric patients less than 12 years of age. Safety, efficacy, and pharmacokinetic profile were similar between adolescent and adult subjects in the pivotal study. A pediatric pharmacokinetic, safety and efficacy PREA Postmarketing Requirement study is ongoing with a planned enrollment of 60 subjects (28 for PK) <12 years of age. Efficacy data can be extrapolated from pharmacokinetic data in pediatric subjects aged 2-11 years to patients <2 years of age. A final pediatric study report will be submitted to the Agency for review.

Post-marketing requirements under FD&C Act section 505(o)

The reviewed safety data do not substantiate a need for a FDAAA post-marketing requirement (PMR) or a Risk Evaluation and Mitigation Strategy (REMS).

d) Recommendation for Postmarketing activities
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 for ages zero to < 12 years**

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 Pediatric Study Plan (PSP) will be a PMR; the adult component will 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 will be a PMR; the adult component will be a PMC.)**