9 November 2017
EMA/CHMP/782768/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Adynovi

International non-proprietary name: rurioctocog alfa pegol

Procedure No. EMEA/H/C/004195/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ABR	annualized bleeding rate
ADME	absorption, distribution, metabolism and excretion
AE	adverse event
AFFF	asymmetric field flow fractionation
AGES	Austrian Agency for Health and Food Safety Ltd.
ALT	alanine transaminase (SGPT)
APC	activated protein C
API	Active Pharmaceutical Ingredient
aPTT	activated partial thrombin time
AS	active substance
AST	aspartate transaminase (SGOT)
$AUC_{0\text{-tlast}}$	area under the concentration versus time curve from 0 to the last sampling time point
AUC0-∞	area under the plasma concentration curve from time 0 to infinity
BAS	bulk active substance
BAX 855	product code name for Baxalta's pegylated recombinant FVIII (rFVIII)
BAX 855 BDS	Rurioctocog alfa pegol, Bulk Drug Substance
BD-rFVIII	B-domain-deleted rFVIII
BDS	Bulk Drug Substance
BEC	Buffer Exchange Chromatography
BEC-E	Re-buffered rFVIII solution (eluate after completion of the BEC step)
BU	Bethesda unit
BVDV	bovine viral diarrhoea virus
BW	body weight
CD	circular dichroism
CEC	Cation exchange chromatography
CHMP	Committee for Medicinal Products for Human Use
CHO	chinese hamster ovary cells
CI	confidence interval

CIOMS	Council for International Organizations of Medical Sciences
CL	total body clearance
Cmax	maximum concentration in plasma
conc	concentration
CPP	Critical process parameter
CQA	critical quality attributes
CSR	clinical study report
DF	diafiltration
DLS	dynamic light scattering
DNA	deoxyribonucleic acid
DoE	Design of Experiments
ECG	electrocardiogram
ED	exposure day (an ED is defined as any calendar day on which at least one infusion of BAX 855 was administered)
ELISA	enzyme-linked immunosorbent assay
FACS	fluorescence-activated cell sorting
FAS	full analysis set
FBS	Foetal bovine serum
FDP	final drug product
FIXa	Activated factor IX
FL-rFVIII	full-length recombinant factor VIII
FP	finished product
FTIR	fourier transform infrared spectroscopy
FVIII	factor VIII
GCP	Good Clinical Practice
GEE	general estimating equation
GLP	good laboratory practice
GMP	Good Manufacturing Practice
h	hour(s)
HAV	hepatitis A virus
HBV	hepatitis B virus
HC	heavy chain
HCP	host cell protein
HCT	hematocrit

HCV	hepatitis C virus
HGB	haemoglobin
HIV	human immunodeficiency virus
HPLC	high performance liquid chromatography
HRQoL	health-related quality of life
ICH	International Committee on Harmonization
i.p.	intraperitoneal
i.v.	intravenous
IgG	immunoglobulin G
IgM	immunoglobulin M
INN	international nonproprietary name
INPT	prothrombin time
IPC	in process control
IR	incremental recovery
IS	international standard
ISE	Integrated Summary/Analysis of Efficacy
ISS	Integrated Summary/Analysis of Safety
ITS	integrated radiotelemetry system
IU	international units
IVR	in vivo recovery
kDA	kilodalton
kg	kilogram
ko	knockout
LBA	ligand binding assay
LC	light chain
LoOI	list of outstanding issues
LoQ	list of questions
LPS	lipopolysaccharide
LRP-1	low-density lipoprotein receptor-1
LRP1	low density lipoprotein receptor-related protein 1
LSC	liquid scintillation counting
MAb	monoclonal antibody
MCB	master cell bank
mg	milligram
MID	minimally important difference
mL	millilitre

MMV	minute virus of mice
MO	major objections
MRT	mean residence time
MTD	maximum tolerated dose
NHS	N-hydroxysuccinimide
Neu5Gc	N-glycolyl neuraminic acid
NOAEL	no observed adverse effect level
µg	microgram
OMCL	official medicines control laboratory
OPE	observation period of efficacy
PedsQL™	Paediatric Quality of Life Inventory™
PEG	polyethylene glycol
PEG-rFVIII	FVIII-bound PEG
PEI	Paul-Ehrlich-Institut
PFA	perfluoroalkyl vinyl ether copolymer
pFMEA	Process Failure Mode and Effects Analysis
Ph.Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PKFAS	pharmacokinetic full analysis set
POSTHOC	posterior conditional estimation
PPAS	per-protocol analysis set
PRO	patient-reported outcome
PTP	previously treated patient
PUP	previously untreated patient
Q1; Q3	quartile 1; quartile 3
QA	quality attributes
QbD	quality by design
rAHF	Recombinant Antihemophilic Factor (other name for rFVIII)
rAHF-PFM	Antihaemophilic Factor (Recombinant), Plasma/Albumin-Free Method
RBC	red blood cell count
Reo-3	reovirus
rFVIII	Recombinant Factor VIII
RS	reference standard

RSD	relative standard deviation, coefficient of variation
SAE	serious adverse event
SAS	safety analysis set
S/D	solvent/detergent
S/D treatment	Solvent/detergent treatment
SD	standard deviation
SDS-PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
SEC	size-exclusion chromatography
SPR	Soy Peptone Reduction
sWFI	sterile water for injections
T1/2	half-life
terminal HL	terminal half-life
TGA	thrombin generation assay
TK	toxicokinetic(s)
Tmax	time to maximum concentration in plasma
TNBP	tri-(N-butyl)-phosphate
TSE	transmissible spongiform encephalopathy
U	units
UF	Ultrafiltration
USP	United States Pharmacopoeia
Vss	volume of distribution at steady state
VWF	Von Willebrand factor
VWF:Ag	Von Willebrand factor antigen
WBA	whole-body autoradiography
WBC	white blood cell
WCB	working cell bank
WFI	Water for Injections
X-MuLV	xenotropic murine leukaemia virus-related virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Baxalta Innovations GmbH submitted on 1 March 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Adynovi, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Adynovi can be used for all age groups.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that rurioctocog alfa pegol was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0001/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0001/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance rurioctocog alfa pegol contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 21 June 2012 and 21 February 2013. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Andrea Laslop Co-Rapporteur: Kristina Dunder

- The application was received by the EMA on 1 March 2016.
- The procedure started on 24 March 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 June 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 June 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 24 June 2016.
- During the meeting on 21 July 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 July 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 13 October 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 November 2016.
- During a meeting of an ad hoc expert group on 28 November 2016, experts were convened to address questions raised by the CHMP.
- During the PRAC meeting on 1 December 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 2 December 2016.
- During the CHMP meeting on 15 December 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 March 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 April 2017.
- During the CHMP meeting on 21 April 2017, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 12 September 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 28 September 2017.
- During the CHMP meeting on 12 October 2017, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 October 2017.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 25 October 2017.
- During the CHMP meeting on 8 November 2017, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 6-9 November 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Adynovi on 9 November 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Haemophilia A is a rare and serious, X-linked, recessive bleeding disorder that predominantly affects males and is characterized by a deficiency of FVIII. In patients with haemophilia A, the primary platelet-driven hemostasis is not affected, but generation of a stable, fibrin-rich clot is defective because inadequate amounts of thrombin are generated. Affected patients suffer from both spontaneous, non-traumatic bleeding episodes as well as substantially prolonged bleeding episodes upon injury. Rarely, life-threatening bleeding may also occur. Patients exhibit variable clinical phenotypes depending on the extent of residual activity (%) of the deficient FVIII that is used to classify the disease severity (WFH, 2012):

- <1% FVIII activity: severe haemophilia A
- 1% to 5% FVIII activity: moderate haemophilia A
- 5% to 40% FVIII activity: mild haemophilia A

Patients with severe haemophilia A bleed spontaneously into joints and muscles, which often results in permanent, disabling joint damage.

2.1.2. Epidemiology

The overall reported number of haemophilia A patients estimated in the 2013 survey by the World Federation of Haemophilia (WFH) included 107 countries with a total population of 6,461,067,861 and identified 140,313 people with haemophilia A (2.2 per 100,000 individuals). There are currently approximately 30,000 patients in the EU with a mean prevalence of approximately 0.6 patients per 10,000.

Haemophilia A is inherited as an X-linked recessive trait and the main risk factors are therefore family history and a carrier mother. Approximately 30% of patients have no family history of the disease; their disease is presumably caused by new mutations.

2.1.3. Biologic features, aetiology and pathogenesis

The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. When infused into a haemophiliac patient, factor VIII binds to von Willebrand factor in the patient's circulation. Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed.

2.1.4. Clinical presentation, diagnosis

Haemophilia A manifests as profuse bleeding into the joints and muscles or internal organs, either spontaneously or as the result of accidental or surgical trauma. Recurrent joint bleeding can lead to chronic arthropathy, pain, and loss of function (Bolton-Maggs and Pasi, 2003). The majority of bleeding occurs internally into joints, most commonly hinged joints such as the ankles, knees, and elbows. Serious bleeds also occur in muscles, especially in deep compartments such as the iliopsoas, calf and forearm, and in the mucous membranes in the mouth, gums, nose, and genitourinary tract. Less frequently, life threatening bleeds can occur in or around vital areas or organs such as the gastrointestinal system or enclosed areas like the intracranial or intracerebral spaces. The approximate frequencies of bleeds at the different sites are: 70 to 80% in joints (haemarthrosis), 10 to 20% in muscle, 5 to 10% in the central nervous system, and < 5% for bleeds at all other sites (Srivastava et al., 2013).

2.1.5. Management

Standard treatment for haemophilia A patients is the replacement of the missing protein by infusion of exogenous FVIII concentrates (as plasma-derived FVIII [pdFVIII] or recombinant FVIII [rFVIII] concentrates). Treatment regimens are either on-demand therapy (given when a bleed occurs) or prophylaxis (which consists of regular infusion of FVIII given every 2 to 3 days to prevent bleeding). In the short term, prophylaxis can prevent spontaneous bleeding and in the long term, prophylaxis can prevent bleeding into joints that will eventually lead to debilitating arthropathy.

Prior to the introduction of clotting factor concentrates in the 1960s, the prognosis for haemophilia A patients was poor, average life expectancy being 15 to 25 years. Major advances in the safety of clotting factor products, including the availability of rFVIII concentrates, the availability of comprehensive haemophilia A treatment centres, the institution of routine prophylaxis, the introduction of home treatment, as well as the active roles that patients take in self-advocacy, have enabled patients with haemophilia A to lead a "close to normal" life.

About the product

Adynovi (INN: rurioctocog alfa pegol) is a pegylated form of Baxalta's licensed full-length recombinant factor VIII ADVATE [octocog alfa] consisting of 2,332 amino acids [molecular weight (MW) 280 kDa]. It is produced by recombinant DNA technology in the Chinese Hamster Ovary (CHO) cell line without the addition of any exogenous human- or animal-derived protein in the cell culture process, purification, pegylation or final formulation. The purified protein is covalently conjugated with a polyethylene glycol (PEG) reagent (MW 20 kDa), predominantly attached to the B-domain of factor VIII.

Adynovi is supplied as powder and solvent for solution for injection together with a reconstitution device.

The Applicant claimed indication:

Adynovi is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Adynovi can be used for all age groups.

Subsequently revised proposed indication:

Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency).

Posology:

The posology for On Demand Treatment is proposed as follows:

The calculation of the required dose of factor VIII is based on the empirical finding that 1 International Unit (IU) factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dl.

The required dose is determined using the following formula: Required units (IU) = body weight (kg) x desired factor VIII rise (%) x 0.5

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

In the case of the following haemorrhagic events, the factor VIII activity should not fall below the given plasma activity level (in % of normal or IU/dl) within the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

Degree of haemorrhage / Type of surgical procedure	**Factor VIII level required (%) (IU/dl)**	**Frequency of doses (hours) / Duration of therapy (days)**
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20 - 40	Repeat injection every 12 to 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleeding or haematoma	30 - 60	Repeat injection every 12 to 24 hours for 3-4 days or more until pain and acute disability are resolved.
Life threatening haemorrhages	60 - 100	Repeat injection every 8 to 24 hours until threat is resolved.
Surgery		
Minor surgery including tooth extraction	30 - 60	Every 24 hours (12 to 24 hours for patients under the age of 6), at least 1 day, until healing is achieved.
Major surgery	80 - 100 (pre- and postoperative)	Repeat injections every 8 to 24 hours (6 to 24 hours for patients under the age of 6) until adequate

		wound healing, then continue therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (U/dl).

For long term prophylaxis, the recommended starting regimen is 40 to 50 IU/kg of Adynovi per kg bodyweight twice weekly in 3 to 4 day intervals. Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency.

Previously untreated patients:

The safety and efficacy of Adynovi in previously untreated patients have not been established. No data are available.

Paediatric patients:

On demand treatment dosing in paediatric patients (12 to 18 years of age) is the same as for adult patients. Prophylactic treatment for patients from 12 to <18 years is the same as for adult patients. Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency.

Method of administration:

Adynovi should be administered as an intravenous infusion. The rate of administration should be determined to ensure the comfort of the patient up to a maximum of 10 ml/min.

2.2. Quality aspects

2.2.1. Introduction

Adynovi (rurioctocog alfa pegol) is an extended half-life pegylated form of the licensed full-length recombinant factor VIII Advate (octocog alfa).

The finished product Adynovi is presented as a powder and solvent for solution for injection containing rurioctocog alfa pegol (INN) as active substance. It is supplied as 250 IU/5 ml; 500 IU/5 ml; 1000 IU/5 ml; 2000 IU/5 ml and 250 IU/2 ml; 500 IU/2 ml; 1000 IU/2ml presentations. Other ingredients are: mannitol; trehalose dihydrate; histidine; glutathione; sodium chloride; calcium chloride dihydrate; tris (hydroxymethyl) aminomethane; polysorbate 80 and water for injections. The product comprises a powder vial and a solvent vial containing 5 ml or 2 ml sterilised water for injections. Adynovi is either supplied with a BAXJECT II Hi-Flow device (CE marked device for reconstitution) or is supplied as an integrated pack containing a ready to use BAXJECT III system in a sealed blister (the powder vial and the solvent vial containing 2 mL solvent are preassembled with the system for reconstitution).

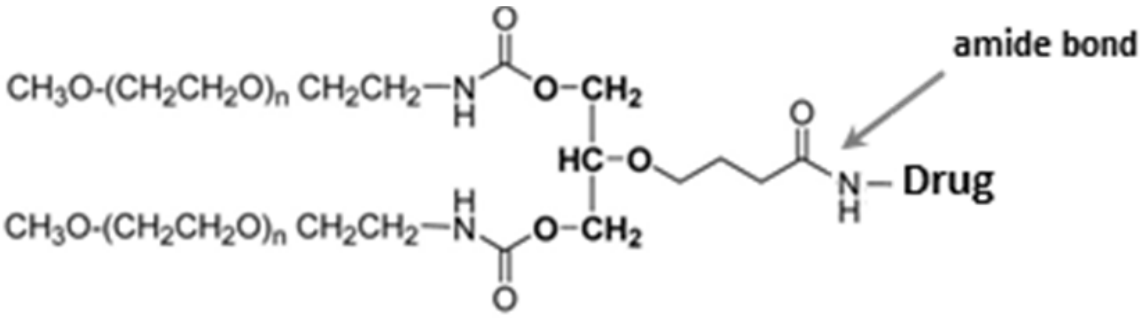
2.2.2. Active Substance

General information

The active substance, rurioctocog alfa pegol (BAX 855) is a human recombinant Factor VIII conjugated with a polyethylene glycol reagent – 20 kDa PEG. More specifically, the recombinant Factor VIII used for the conjugation is the active substance (octocog alfa, also termed Advate bulk active substance (BAS)) of Baxalta's licensed medicinal product ADVATE. ADVATE is therefore an intermediate of the Adynovi active substance (AS), rurioctocog alfa pegol.

The average molecular mass of rurioctocog alfa pegol is approximately 330 kDa of which the protein moiety constitutes approximately 280 kDa. Rurioctocog alfa pegol contains recombinant coagulation Factor VIII, a purified glycoprotein that has 2332 amino acids. The protein bears a number of post-translational modifications including more than 20 glycans, most of which are located on the B domain. The amino acid sequence is comparable to human Factor VIII, and the post-translational modifications are similar to those of the plasma-derived molecule. The 20 kDa PEG polymer used consists of a branched structure with 2 symmetric PEG chains with 10 kDa each connected to a glycerol backbone. The PEG-FVIII conjugate is linked via a stable amide bond to the protein lysine side chain residues.

Figure 1. Chemical structure of PEG drug conjugate



Manufacture, characterisation and process controls

Rurioctocog alfa pegol active substance (AS) is manufactured by Baxalta US, Inc.. Release testing sites are specified in the dossier.

Description of manufacturing process and process controls

The first step of the rurioctocog alfa pegol manufacturing process is the production of the intermediate octocog alfa (rFVIII, termed ADVATE bulk active substance BDS), which is synthesized in a CHO cell line. During the cell culture process Factor VIII is produced and secreted into the medium. The recovery and purification process consists of filtration and chromatography steps as well as an S/D (solvent detergent) virus inactivation step.

The process to produce one batch of the AS intermediate (Octocog alfa) has been defined.

The octocog alfa containers are stored under defined conditions (temperature, time). In-process monitoring and controls, including controls for microbial purity and endotoxin, are valid and are suitably described.

Octocog alfa is then used for further manufacturing to the rurioctocog alfa pegol AS. The rurioctocog alfa pegol AS production process to produce one rurioctocog alfa pegol AS batch has been defined.

The process includes a PEGylation and chromatography steps prior to formulation. Shipping conditions have been adequately validated.

The manufacturing process and process controls for octocog alfa pegol are suitable. The active substance manufacturing process is therefore considered acceptable.

Control of Materials

The expression system chosen to produce recombinant Antihemophilic Factor, Plasma/Albumin Free Method (rAHF-PFM), is the same as ADVATE and involves the sequential introduction and amplification of rAHF and recombinant von Willebrand Factor (rvWF) genes in a CHO cell line. The resulting cell line (10A1C6) is used to produce the licensed product ADVATE. The entire hFVIII gene has been previously sequenced.

A two tiered cell banking system is used and sufficient information has been provided regarding testing of master cell bank (MCB) and working cell bank (WCB). Genetic stability has been demonstrated for cells. New WCBs are established according to an agreed protocol. All raw materials used for cell bank preparation and fermentation as well as for the purification of the active substance have been listed. Information on the quality and control of the listed raw materials has been provided. A detailed description of the cell line derivation, preparation and characterisation of the cell bank system and manufacturing process has been provided.

Control of critical steps and intermediates

The Critical Quality Attributes (CQAs) and Quality Attributes (QAs) have been defined and are listed in the dossier. Critical process parameters (CPPs) were defined and the related operating ranges are documented in several development study reports and transferred to manufacturing documents.

Specifications with acceptance criteria for identity, purity and potency are in place and are considered appropriate for quality control release of the intermediate octocog alfa.

Information on the PEG reagent has been presented and information on its manufacturing process, characterisation data, specification and stability data has been presented. The establishment of the control strategy is acceptable.

Process validation

Process validation has been conducted for the complete AS manufacturing process. Multiple bulk active substance batches have been used for process validation. The presented process validation data are acceptable.

For the subsequent steps to produce the AS, the performed process validation activities are considered appropriate to ensure that the manufacturing process operates within established parameters and can perform effectively and reproducibly to deliver active substance material meeting its predetermined specifications and quality attributes. This process validation consisted of multiple commercial-scale and process rurioctocog alfa pegol batches.

Process-related as well as product-related impurities in the Advate bulk active substance have been appropriately discussed (see characterisation section for more information). The provided data demonstrate the removal of these impurities to sufficiently low levels. For a subset of the discussed impurities, specifications with appropriate acceptance limits during routine production are in place. Stated impurities have been present in product tested in clinical trials

Manufacturing process development

The Manufacturing process development history throughout clinical development has been described.

Octocog alfa from the all manufacturing sites has been used during development. It has been shown that rurioctocog alfa pegol batches produced with octocog alfa derived from all facilities are comparable.

Since process changes were implemented in the manufacturing process for the octocog alfa, a thorough evaluation of the comparability of the octocog alfa between manufacturing changes as well as the comparability of the rurioctocog alfa pegol manufactured from octocog alfa manufactured with the modified process was performed. Structural and functional characterization showed that the process changes implemented during development did not impact product characteristics and confirmed process consistency.

Comparability studies demonstrated consistency, stability and reproducibility of the rurioctocog alfa pegol process over time. Conducted process robustness studies confirmed that the described manufacturing process is suitable for the production of PEGylated Factor VIII having a consistent product quality

Characterisation

Characterisation has been carried out on an appropriate number of batches of rurioctocog alfa pegol . Characterisation of octocog alfa as provided is based on the information included in the respective ADVATE Marketing Authorisation (MA). A large panel of “state-of-the-art” methods has been used to address primary and higher-order structures, size, protein composition and pegylation analysis, post-translational modifications, purity and the impurity profile as well as the biological activity.

Process and product-related impurities which can be present in the active substance have been identified. Impurities derived from the manufacturing of the intermediate rFVIII (ADVATE process) have been discussed. Aggregates are routinely analysed. A discussion on the genotoxic potential of all materials/impurities involved in the synthesis of the PEG reagent on the basis of their chemical structure has been provided and all are considered to be non-mutagenic.

Specification

The specifications include suitable test methods for identity, purity and potency .The limits for potency determination by both chromogenic and clotting assay have been adapted

Analytical Methods

Method descriptions as well as validation summaries and detailed reports have been provided.

Batch analysis

Batch analyses data have been provided for all manufacturing sites. Batch data of active substance produced for nonclinical, clinical, conformance (commercial process and scale lots produced at the commercial facility) and stability program have been presented. Overall, these data support the conclusion that the manufacturing process at all three sites is capable of delivering material of consistent high quality.

Reference Materials

A narrative description of the reference standards for testing of potency and total protein has been provided. Also the reference material for Western blotting and a pegylation reagent standard for testing of free PEG (in AS) and total PEG (in AS and FDP) has been described.

A major objection was raised on the potency standard regarding its calibration, its relationship to the international standard and the suitability of the proposed potency assays for release purposes. During the procedure, the applicant directly calibrated the standard to the international standard and provided further information about the potency assignment.

However, as a post-marketing commitment, the applicant is recommended to review the potency specification limits in line with manufacturing experience.

Stability

The AS stability studies were carried out in accordance with ICH guidelines. The container closure system is representative of that used for commercial material. The relevant attributes of the AS were adequately addressed by appropriate stability-indicating tests in the analytical program.

This shelf-life claim is based on stability data from clinical phase 2/3 batches and conformance batches (process validation lots). The stability data support the shelf-life claim.

Note that the current licensed storage condition for the octocog alfa intermediate is as approved in the Advate MA.

2.2.3. Finished Medicinal Product-- Adynovi- powder FP

Description of the product and pharmaceutical development

The finished product is presented as a powder and solvent for solution for injection rurioctocog alfa pegol (INN) as active substance. It is supplied as 250 IU/5 ml; 500 IU/5 ml; 1000 IU/5 ml; 2000 IU/5 ml and 250 IU/2 ml; 500 IU/2 ml and 1000 IU/2 ml product presentations. Other ingredients are: mannitol; trehalose dihydrate; histidine; glutathione; sodium chloride; calcium chloride dihydrate; tris (hydroxymethyl) aminomethane; polysorbate 80 and water for injections. All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The product comprises a powder vial and a solvent vial containing 5 ml or 2 ml sterilised water for injections.The vials are of type I glass closed with chlorobutyl rubber stoppers. The material complies with Ph. Eur. and EC requirements. Container-closure integrity has been demonstrated and extractables/ leachables satisfactorily investigated.

Component	**Function**				
BAX 855 Drug Substance - PEGylated recombinant human FVIII	Active Pharma-ceutical Ingredient (API)	**250 IU**	**500 IU**	**1000 IU**	**2000 IU**
Mannitol	Bulking agent				
Trehalose dihydrate	Bulking agent				
Sodium chloride	Tonicity modifier				

Component	Function
Histidine	Buffering agent
Tromethamine / Trometamol [Tris(hydroxymethyl)-aminomethane]	Buffering agent
Calcium chloride dihydrate	Stabilizing agent
Polysorbate 80	Surfactant
Glutathione	Antioxidant

Pharmaceutical development

The pharmaceutical development of the finished product has been comprehensively described. The final chosen formulation has been sufficiently justified. The same formulation as for the product Advate was chosen and this same formulation was used for preclinical studies as well as for the different clinical phases.

The manufacturing process transfer between sites has been justified for Adynovi FP. Despite these differences in manufacturing location during development, there were no changes in the formulation used for preclinical and clinical Phase 1 and Phase 3 lots. No major changes of the process have been introduced. The description of the development of the lyophilisation process is comprehensive including state-of-the-art techniques. Characterisation showed that the quality of the materials used in the clinical trial is comparable. The development of the container closure system has been acceptably described including the compatibility with the two different reconstitution systems chosen (BAXJECT II HF and BAXJECT III). In conclusion, AS and FP manufactured according to the commercial process has been used in phase III studies.

Reconstitution system

The finished product Adynovi (BAX 855) can alternatively be supplied with the BAXJECT II Hi-Flow Needleless Transfer Device or the BAXJECT III Reconstitution System. The BAXJECT II Hi-Flow device is a CE marked product.

Unlike the BAXJECT II Hi-Flow device, BAXJECT III system is an integrated reconstitution system consisting of a product vial, a diluent vial and a transfer set; the respective vials are pre-assembled to the BAXJECT III unit and the integrated system is provided to the user in a single blister pack. Comprehensive information about the material used in comparison with the CE marked system as well as qualification of the system has been provided.

Manufacture of the product and process controls

The finished product is manufactured by Baxalta Manufacturing S.à.r.l.. Baxalta Belgium Manufacturing S.A serves as the final batch release entity.

After the manufacturing operations required to produce AS (i.e. PEGylated recombinant human Factor VIII) have been performed, it is shipped to the FP facility for FP manufacture.

The batch size of finished product has been defined.

The finished product manufacturing process consists of the formulation of active substance, followed by sterile filtration, aseptic filling, lyophilisation, capping, bulk packaging and storage before shipment of the finished product between facilities for labelling and packaging. The manufacturing process has been described in sufficient detail. No reprocessing is foreseen.

Critical quality attributes (CQA) and critical process parameters (CPPs) were identified and then used during clinical development to establish manufacturing controls and limits and to evaluate the impact of manufacturing process changes prior to implementation. For the validation of the manufacturing process, an appropriate validation approach has been used. The manufacturing process is similar to the one performed to produce Advate FP. All conformance (validation) batches met the acceptance criteria for the finished product specification.

Validation and evaluation studies were also performed to demonstrate that manufacturing operations consistently produce safe and effective BAXJECT III Systems that meet predetermined specifications and quality attributes. BAXJECT III system is validated with Adynovi FP and found acceptable to show suitability for the intended use. Shipping validation studies have been performed and are appropriate.

Product specification

For some of the test parameters tightening/ clinical justification was requested. Impurities do not differ in AS and FP. During production of Adynovi, only mannitol and trehalose are added to the AS and no additional process-related impurities are anticipated. The agreed FP specification limits, based on the process capability and evaluation of available clinical results include appropriate specifications for identity, purity and potency.

For both potency assays a new in-house reference standard, calibrated against the WHO 8th IS was introduced and appropriate specification limits for both potency assays were established.

Analytical methods

The analytical methods have been sufficiently described. Non-pharmacopoeial methods have been validated according to ICH Guidelines. Issues related to the potency assays raised during the procedure and included in the remaining major objection at Day 180 were subsequently suitably addressed. Concerning the chromogenic method used, the CMHP has recommended further information to be provided post-authorisation regarding planned improvements to this assay and review of potency specification limits, as needed.

Batch analysis

A large number of batch data for non-clinical and clinical development finished product batches as well as for at least three conformance batches (process validation) are provided. All final finished product lots were tested according to finished product specifications at time of manufacture and release of the batches. The analyses data of batches manufactured in all facilities showed that all batches met the acceptance criteria and confirm consistency of the manufacturing process. Furthermore, batch data from conformance batches with the reconstitution system BAXJECT III to verify comparability with batches without this system are acceptable.

Reference materials

Suitable information on reference standards which are used for the release and stability testing of AS and FP have been provided. See active substance ‘reference materials’ section and ‘analytical methods’ in the finished product section for further information on the reference standard.

Stability of the product

A FP shelf-life of 24 months following storage at +5°C ±3°C, which includes a three month storage period at up to +30°C, is proposed. After storage at +30°C, the product must not be returned to the refrigerator. Stability studies were conducted in line with ICH guidelines in containers identical to those proposed for marketing. Based on available stability data, the shelf-life and these storage conditions, as stated in the SmPC are acceptable.

To date, long-term stability data (+5°C) have been presented for the conformance batches.

The stability-indicating quality attributes used to monitor the stability are a subset of the FP release specifications.

Results from conformance batches for the four strengths (250, 500, 1000 and 2000 IU/vial) are presented.

Also data from clinical batches are provided, which can be considered as supporting data.

Satisfactory data to support storage of the finished product for up to three months at 30°C after long-term storage of 21 months at +5°C have been provided. The conducted photostability study, in line with ICH Q1B, showed that the AS protein is not prone to photo-degradation.

Chemical and physical in use stability has been demonstrated for three hours at a temperature not above 30 °C. From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately.

A FP shelf-life of 24 months following storage at +5°C ±3°C, which includes a three month storage period at +30°C, is agreed.

Adventitious agents

The viral validation studies performed for Advate are fully applicable to the Adynovi product and no animal- or human-derived substances are added during the PEGylation process or used in the manufacture of FP. Therefore, the adventitious agents' safety evaluation of the licensed product Advate is fully applicable to Adynovi. In the course of the manufacture of octocog alfa, a series of chromatographic steps and solvent/detergent treatment have been validated for virus inactivation/ removal.

For the manufacture of octocog alfa, the biological material used during purification has been adequately evaluated from a viral/TSE perspective. Overall, the manufacturing process for Adynovi provides for an acceptable margin of safety, of the final product with respect to adventitious viruses.

2.2.4. Finished Medicinal Product-- Adynovi- solvent FP

Description of the product and pharmaceutical development

The sterile Water for Injections (WFI) is supplied in 2mL and 5 mL presentations, There are no other constituents in the formulation. The solvent is supplied in a Type I (Ph. Eur.) glass vial with a chlorobutyl stopper (complying with Ph. Eur.). Container-closure integrity was demonstrated and an extractable-leachable study was conducted.

The manufacturing process described is unchanged from the process used during development. Stability data indicate that the sterile Water for Injections (sWFI) is compatible with the vial and stopper. Data on compatibility

of the sWFI with the lyophilised finished product has been provided in the stability section for the lyophilised finished product.

Manufacture of the product and process controls

The manufacturing process for sterile Water for Injections (sWFI) consists of seven main steps: equipment preparation, compounding, filtration, filling, autoclaving, visual inspection, labeling and packaging. These main steps are regarded as critical and a number of process control tests are performed to control the manufacturing process.

Product specification

The specifications for the fill volumes 2 and 5 ml are identical except for the limit for extractable volume. The specification includes appropriate identity and purity tests

Analytical methods

The analytical methods are based on both the USP monograph for sterile Water for Injections and the European Pharmacopoeia monograph for sterilised Water for Injections (0169).

Batch analysis

Satisfactory batch analysis data are presented in the dossier

Stability of the product

Based on the real time stability data presented, the proposed shelf life of 5 years (5 ml) and 3 years (2 ml) when stored at 2 – 8°C is acceptable.

2.2.5. Discussion on chemical, pharmaceutical and biological aspects

Advate bulk active substance (octocog alfa, which is the active substance of the EU licensed Advate, is used for further processing (pegylation with a 20 kDa activated PEG) to the rurioctocog alfa pegol. The manufacturing process has been adequately described; the proposed process control strategy and the performed process validation activities are considered appropriate to ensure that the manufacturing process operates within established parameters and can perform effectively and reproducibly to deliver active substance material meeting its predetermined specifications and quality attributes. Presented batch data further support this conclusion and do not raise any concerns related to the quality of AS. Specifications for release and stability testing are acceptable

The applicant changed to the chromogenic method for release purposes. However, as a post-marketing commitment, the applicant is recommended to provide additional information regarding the planned improvements to the assay and review the potency specification limits in line with manufacturing experience.

2.2.6. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product

have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.7. Recommendation(s) for future quality development

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends points for investigation as detailed in the report.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary pharmacodynamics of Adynovi were assessed in one *in vitro* () and two *in vivo* studies (), please see table below:

Table 5 Summary of primary pharmacodynamics of Adynovi:

Pharmacodynamic Model	Species/ Strain	Method of Administration	Doses IU FVIII/kg	Gender and No. Per Group	Noteworthy Findings	GLP[a]
activated Partial Prothrombin Time (aPTT) assay for pharmacological activity in vitro	Plasma of Rat, Cynomolgus Monkey, Human	In vitro	1, 5 and 10 IU FVIII/mL	n.a.	A dose-dependent reduction of the activated partial thrombin time in plasma from rats, cynomolgus monkeys and humans was shown	No
Tail Tip Bleeding	E17 FVIII ko mouse	Intravenous	200	8M/8F	Prolongation of clinically relevant efficacy in comparison with ADVATE	No
Carotid Occlusion	E17 FVIII ko mouse	Intravenous	200	6M/6F	Prolongation of clinically relevant efficacy in comparison with ADVATE	No

[a] GLP = Good Laboratory Practices
n.a. = Not applicable

Effects of Adynovi on the coagulation system in terms of activated Partial Thromboplastin Time (aPTT) were studied *in vitro* in plasma from rats, *Cynomolgus* monkeys and humans at a clinically relevant concentration and above. A dose dependent reduction of aPTT time was observed for all 3 species which indicates that Adynovi is pharmacologically active in humans and in rats and *Cynomolgus* monkeys, the 2 species used for general toxicological studies. No data on the effect of Adynovi on aPTT in plasma from mice and rabbits, also used in the toxicological evaluation, were submitted. Due to the type of pharmacological effect Adynovi is however expected to be pharmacologically active also in mice and rabbits. Although a comparison with Advate for evaluation of the effect of PEGylation on aPTT would have been valuable, this is not considered critical as the pharmacological effects of Adynovi and Advate were compared in animal *in vivo* studies and the effect of Adynovi is confirmed in clinical studies.

The effects of Adynovi and Advate on blood coagulation system reflected by reduced tail tip bleeding and induction of carotid occlusion were studied *in vivo* in E17 FVIII knock out mice (exon 17 ko mice; strain B6;129S- F8tm2Kaz/J) lacking coagulation factor VIII. The results (reduced blood loss in the Tail Tip Bleeding study and decreased time to permanent vessel occlusion in the Carotid Occlusion study for Adynovi and Advate) should be interpreted with caution due to high variability and/or small sample size. However, they are considered sufficient to conclude that both models indicate a prolonged efficacy of Adynovi in comparison to Advate.

Secondary pharmacodynamic studies

No dedicated studies on secondary pharmacodynamics were submitted.

Safety pharmacology programme

The thrombogenic potential of Adynovi and its effects on body temperature, cardiovascular (aortic blood pressure and single lead electrocardiogram (ECG)), and respiratory (intra-thoracic pressure) parameters were investigated in 2 GLP-compliant in vivo studies in rabbits and cynomolgus monkeys, please see table below:

Table 6 Summary of safety pharmacology studies for Adynovi

Pharmacodynamic Model	Species/ Strain	Method of Administration	Doses IU FVIII/kg	Gender and No. Per Group	Noteworthy Findings	GLP[a]
Thrombogenic Potential	Rabbit/NZW	Intravenous	900	3M/3F	No thrombogenic potential	Yes
Cardiovascular Effects (Telemetry)	Cynomolgus Monkey	Intravenous	150, 600	8M	No adverse cardiovascular or respiratory effects	Yes

[a] GLP = Good Laboratory Practices; NZW = New Zealand White

No thrombogenic potential or effects on the cardiovascular or the respiratory system were observed in the safety pharmacology studies following single IV administrations of 900 IU/kg Adynovi in rabbits and 150 and 600 IU/kg Adynovi in *Cynomolgus* monkeys.

No studies on toxicokinetics were provided but an exposure in terms of FVIII activity up to approximately 115 h*IU/ml for AUC0-tlast and 12 IU/ml for Cmax can be extrapolated to the cardiovascular and respiratory safety pharmacology study in monkeys from the single dose escalation study of Adynovi in *Cynomolgus* monkeys. This is above the expected therapeutic exposure in patients.

As no adverse behavioural effects or clinical observations were observed in the cardiovascular and respiratory safety pharmacology study in C*ynomolgus* monkeys no specific CNS safety pharmacology study was provided.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies have been performed.

2.3.3. Pharmacokinetics

The pharmacokinetics (PK) of Adynovi were evaluated based on FVIII activity, FVIII levels and PEGFVIII (Adynovi) levels in single dose studies following intravenous administration to E17 FVIII knock out (ko) mice (with haemophilia of a severe phenotype (<1% FVIII residual activity)), normal rats and *Cynomolgus* monkeys.

The primary endpoints in the pharmacokinetic studies were AUC0-tlast to evaluate the bioavailability of Adynovi and the MRT to describe a potential extension of circulation time in blood.

Table 7 A summary of the pharmacokinetics studies performed with PEGylated FVIII (Adynovi)

Type of Study	Test System	Method of Administration
Absorption After Single Dose	Mouse E17 FVIII ko	Intravenous
	Rat Crl: CD(SD)	Intravenous
	Cynomolgus monkey[c]	Intravenous
Absorption, Distribution, Metabolism, Excretion (ADME)	Rat Sprague Dawley	Intravenous

Methods of analysis

Regarding the methods of analysis, different methods were used for the characterisation of the pharmacokinetic profile of Adynovi in rat, *Cynomolgus* monkey and E17 mouse plasma such as the FVIII activity chromogenic assay, the FVIII: Antigen ELISA and the PEG-factor FVIII ELISA.

Absorption

In E17 FVIII ko mice, an increase of AUC0-tlast with Adynovi to almost the double of the AUC0-tlast observed with Advate could be shown. The MRT indicated a prolongation of 1.6 times in FVIII activity with the Adynovi compared to Advate (7.9 vs. 4.9 hours).

In Sprague Dawley rats, single administration of Adynovi showed that FVIII antigen dose-adjusted AUC0-tlast was 1.4 times higher after infusion of Adynovi than after infusion of Advate. The MRT for FVIII antigen was prolonged by the factor 1.2 after Adynovi administration compared to Advate. No consistent deviation from a dose proportional increase in exposure of FVIII antigen or PEG-FVIII was indicated at the studied dose range of 200, 350 and 700 IU/kg.

The pharmacokinetic profile of *Cynomolgus* monkeys showed a prolonged FVIII exposure with Adynovi in comparison to Advate. The AUC0-tlast for Adynovi was 1.3 times larger than for Advate after two administrations of 350 IU FVIII/kg at day 1 and day 8.

With regards to FVIII activity the increase of AUC0-tlast per doubling dose of Adynovi in IU/kg for the dose range investigated (350, 700 and 1500 IU FVIII/kg) was 1.51 and 1.85, respectively, for the two investigated lots indicating a dose-proportional increase for one lot and a sub-proportional increase for the other lot. Similarly, increases in the AUC0-tlast of FVIII-bound PEG were 1.47 or 2.0, respectively.

Distribution, Metabolism and Excretion

Concerning absorption, distribution, metabolism, and elimination radiolabelled Adynovi was examined following a single intravenous administration in rats. There were minimal gender differences in pharmacokinetic parameters, with males showing a longer half-life, while exposure to drug derived radioactivity remained similar. The radiolabelled test item was distributed with highest concentrations of radioactivity observed in the plasma, blood, mesenteric lymph nodes, spleen, liver, adrenal glands, and kidneys. Distribution of [3H]PEG-rFVIII derived radioactivity to the brain, a tissue of high concern for PEGylated compounds, was shown

but the levels were lower than in other tissues and no CNS toxicity was indicated in the toxicological studies in adult animals. Radioactivity was cleared from circulation with half-lives of at least 276 hours (plasma, females), with elimination primarily via urine. The mean overall recoveries indicate a quantitative excretion at 1008 hours after single dose injection.

Pharmacokinetic drug interactions

No nonclinical drug interaction studies were performed.

Other pharmacokinetic studies

No other PK studies have been performed.

2.3.4. Toxicology

The nonclinical development plan for Adynovi included *in vitro* and *in vivo* toxicity studies.

Study Type and Duration	Route of Administration	Species
Single Dose Toxicity (Escalating Dose Study)	intravenous	Cynomolgus Monkey
Repeat Dose Toxicity (1 month)	intravenous	Rat
		Cynomolgus Monkey
Local Tolerance	intravenous intraarterial paravenous	Rabbit
Immunogenicity in vivo	intravenous	Mouse Cynomolgus Monkeys
Immunogenicity in vitro	-	Human Whole Blood Human Plasma
Tissue Cross Reactivity in vitro	-	Human tissue

Single dose toxicity

No single dose toxicity studies have been performed. However, a dose-escalation study with *Cynomolgus* monkeys was performed with Adynovi.

Repeated dose toxicity

The nonclinical development plan for Adynovi included *in vitro* and *in vivo* toxicity studies.

Repeated dose toxicity studies of Adynovi were assessed in rats and *Cynomolgus* monkeys.

In the repeated dose toxicity study in rats, animals were dosed intravenously with 350 or 700 IU FVIII/kg Adynovi (2 lots) every other day over 29 days (15 doses) followed by a 2 week recovery period.

No thrombotic events and no treatment related changes were noted up to 700 IU FVIII/kg. Therefore, the No Observed Adverse Effect Level (NOAEL) was set at 700 IU FVIII/kg after 15 injections every other day for a time period of 29 days.

In a pilot toxicity study in *Cynomolgus* monkeys, treatment with Adynovi was well tolerated at 700 IU/kg during the repeated dose phase and did not reveal any adverse clinical symptoms or findings that could be attributed to the test item. The NOAEL for the repeated dose phase of this study was 700 IU FVIII/kg under the conditions of this study.

The observed findings were likely of pharmacological nature and resulted in a transient increase of thrombin-antithrombin fragments, an increase of D-dimers, and shortening of the activated partial thromboplastin time in single animals at single time points. During the repeated dose phase there was a prolongation of aPTT which was possibly related to the formation of neutralising anti-FVIII antibodies.

Slightly elevated liver enzymes during the escalating dose phase are believed to be of transient nature and did not result in toxicologically relevant findings. There were no findings in serum chemistry or haematology parameters throughout the repeated dose phase that were considered to be test item-related.

In a pivotal repeat dose toxicity study in *Cynomolgus* monkeys (Study 1933-018) 2 lots of Adynovi at dose levels of 150, 350 or 700 IU FVIII/kg were administered intravenously to the animals every 5 days for a period of 4 weeks (6 applications in total). The assessment of toxicology was based on body weight determination, clinical signs, ophthalmic examinations, haematology, coagulation, clinical chemistry, urine analysis, macroscopic findings at necropsy and histopathological findings; toxicokinetics and antibody assessment were also included.

Treatment with Adynovi was well tolerated at either dose and did not reveal any adverse clinical symptoms or findings that could be clearly attributed to the test item. No vacuoles were found in the choroid plexus of Adynovi exposed animals. However, two animals showed vacuolation in the kidney in the mid dose group (350IU), which did not recover after 2 weeks. Renal safety is further discussed in the clinical part of the assessment report.

The formation of antibodies against Adynovi is an expected immune reaction after repeated application of heterologous proteins to *Cynomolgus* monkeys, which is also well known for non-pegylated FVIII products. Thus, the NOAEL for this study was the high dose of 700 IU/kg under the conditions of this study.

Interaction of Adynovi activity with the coagulation system was shown in an *in vitro* assay demonstrating a dose-dependent reduction of the activated partial thrombin time in plasma from cynomolgus monkeys, rats and humans.

In repeated dose toxicity studies in rats and *Cynomolgous* monkeys no macroscopic, microscopic or clinical findings suggestive of CNS toxicity were observed at any time point during the studies.

Genotoxicity

Genotoxicity studies were not submitted (see discussion on non-clinical aspects).

Carcinogenicity

Carcinogenicity studies were not submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

Reproduction studies were not submitted (see discussion on non-clinical aspects).

Local Tolerance

Local tolerance was assessed during repeated dose toxicity studies in rats (Study 8202366) and *Cynomolgus* monkeys (Study 1933-018). Microscopic findings at injection sites of animals were comparable with controls and were consistent with a normal response expected after intravenous injection.

One additional study in rabbits was performed to investigate local tolerance of Adynovi at a potency of 2000 IU FVIII/5 mL vial (Study PV2651201). The aim of the study was to assess local tolerance of BAX 855 with a nominal potency of 2000 IU FVIII/5 mL vial after intravenous (clinical application route), intra-arterial and para-venous (possible misapplication routes) application in rabbits. Adynovi (nominal potency of 2000 IU FVIII/5 mL vial) was compared with Advate, the currently licensed rFVIII product at a nominal potency of 2000 IU FVIII/5 mL vial and the corresponding formulation buffer for Adynovi (also used as formulation buffer for ADVATE, vehicle control) and saline (negative control).

No alterations in behaviour were seen during the observation period in any of the treated animals. Macroscopic examination revealed no visible changes after administration of Adynovi (nominal potency of 2000 IU FVIII/5 mL vial) for any administration route. Histopathologically, no adverse lesions with regards to local tissue tolerability of the test item were detected.

Immunogenicity

Immunogenicity of Adynovi was evaluated in comparison with the unmodified Advate, as any chemical modification of FVIII may alter its immunogenic potential. Different comparative immunogenicity studies (*in vitro* in human plasma and whole blood as well as *in vivo* in mice and monkeys) were performed to assess the potential impact of Adynovi and Advate on both the innate and the adaptive immune system.

As expected for a heterologous human protein drug, repeated doses of Adynovi resulted in the formation of anti-drug antibodies specific for human FVIII or PEG and neutralising for FVIII activity in animal models. Repeated dose toxicity studies in rats and *Cynomolgus* monkeys have shown that antibodies specific for human FVIII were induced in rats and monkeys. The anti-FVIII antibodies showed neutralising properties against FVIII activity and against PEG-FVIII.

As a consequence, systemic exposures to Adynovi was substantially lower following repeated dose administration (Day 29) as compared to those following single dose administrations (Day 1), regardless of gender or dose administered.

Two different lots of Adynovi containing different aggregate levels expressed a similar immunogenicity profile in 2 haemophilic mouse models. Adynovi induced anti-PEG antibodies only in mice that recognise FVIII as immunogenic foreign protein indicating that only patients who recognise FVIII as foreign structure may be at risk for developing antibodies against PEG after treatment with Adynovi.

Results obtained demonstrate that Adynovi and Advate have a similar immunogenicity profile.

Adynovi was well tolerated after intravenous (intended clinical administration route) intra-arterial and para-venous administration, up to a nominal potency of 2000 IU FVIII/5 mL vial, as tested in a local tolerance study performed in rabbits (PV2651201).

In addition, potential cross reactivity of high affinity anti-PEG antibodies with human tissues was investigated in a tissue cross reactivity study and showed no findings.

PEG

PEG is an inert molecule and not metabolised by enzymes. Based on its stable properties, PEG and PEG containing drugs may cause vacuolation of certain cell types after treatment with high parenteral doses, as observed under histopathological examination of animal organs in previous studies (Ivens *et al*, 2012).

Focusing on possible safety issues that could arise from the modification with PEG, the Applicant provided a repeated dose toxicity study in rats with intravenous administration of PEG2ru20KCOOH, a toxicological relevant unbound 20kD PEG model.

Considering a PEG dose of 0.095 µg per IU FVIII, the maximum anticipated long-term prophylactic dose of 80 IU FVIII/kg results in a single PEG application of 7.6 µg/kg Body Weight. Thus, the highest dose used in this study (65 mg/kg) covered approximately the 8552-fold of the worst case clinical PEG exposure / day.

The PEG polymer without the FVIII protein part was well tolerated in rats and did not show any signs of toxicity even at the highest dose tested. In view of PEG-related findings, such as vacuolation of macrophages or other cells, reported in the literature, a detailed histopathological examination of the brain (including choroid plexus) and of the spinal cord has been conducted in this study by the Applicant.

The cumulative PEG dose is important in considering possible accumulation and vacuolation of ependymal cells *in vivo*. The PEG exposure anticipated in the clinical setting is 105 times lower than the threshold for ependymal cell vacuolation observed in animal studies (≥ 0.4 µmol/kg/month).

2.3.4. Ecotoxicity / environmental risk assessment

Adynovi is a recombinant replacement protein of the naturally occurring coagulation factor VIII. It is catabolised during human metabolism and no active molecule is excreted by the patient. In accordance with the guideline CHMP/SWP/4447/00 (1), Adynovi as a protein is exempted from an environmental risk assessment since proteins are unlikely to result in a significant risk to the environment.

However, the Applicant provided an environmental risk assessment (ERA) and presented evidence for the absence of need for further screening on the persistence and bioaccumulation potential of the drug substance PEG-rFVIII conjugate.

Substance (INN/Invented Name):	Rurioctocog alfa pegol (Pegylated recombinant human factor VIII)		
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	Log K_{ow} = -0.698 (PEG, CAS 25322-68-3)	Potential PBT = NO
	OECD 107	Log K_{ow} = -1.98 (PEG-Interferon beta 1a)	
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)	$1.77 \cdot 10^{-05}$	µg/L	> 0.01 threshold NO

The Adynovi PECsurfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as Log Kow of PEG and PEGylated protein do not exceed 4.5.

Therefore, Adynovi is not expected to pose a risk to the environment.

2.3.5. Discussion on non-clinical aspects

The nonclinical development program was designed to evaluate the pharmacology, pharmacokinetics and toxicology and immunogenicity of Adynovi in support of the Marketing Authorisation.

Pharmacology

Regarding primary pharmacodynamics, a dose-dependent reduction of the activated partial prothrombin time by Adynovi could be demonstrated *in vitro* in human, rat and monkey plasma.

In vivo a prolonged efficacy of Adynovi in comparison to ADVATE could be shown in both pharmacodynamics models (tail tip bleeding and carotid occlusion) performed in E17 FVIII ko mice. Study data revealed that Adynovi was similarly efficacious to Advate when administered at ≥ 1.5 times longer treatment intervals than Advate.

According to guideline ICH S7 A "Safety Pharmacology Studies for Human Pharmaceuticals" secondary pharmacodynamic studies are defined as "studies on the mode of action and/or effects of a substance not related to its desired therapeutic target". In the nonclinical studies of Adynovi, no effects other than those induced by the primary action of Adynovi, i.e. interaction with the blood coagulation, were observed. Hence, no dedicated studies on secondary pharmacodynamics were submitted. Since unPEGylated rFVIII is a known active substance which interacts specifically with the intrinsic coagulation system, the lack of secondary pharmacodynamic studies is accepted. Potential adverse effects of the PEGylated rFVIII would be expected to be detected in the safety pharmacological studies and the toxicological studies performed.

Safety pharmacology

Results of safety pharmacology studies evaluating the thrombogenic potential (rabbits) and the toxicity (4-week toxicity studies in monkeys and rats) did not raise any safety concerns.

Various types of PEG have however been reported to induce adverse effects such as vacuolisation in the CNS. Investigation of potential CNS effects is therefore of utmost importance for a PEGylated product as Adynovi. No findings indicative of histopathological changes of Adynovi or unconjugated 20 kDa PEG in the brain or spinal cord were reported in toxicological studies in *Cynomolgus* monkeys and rats, i.e. there were no signs of potentially test-article related cell vacuolisation in the CNS of adult animals. However no dedicated CNS safety pharmacology single dose studies were performed.

Pharmacokinetics

The pharmacokinetic profile of Adynovi was evaluated in E17 ko mice, in rats and in *Cynomolgus* monkeys after intravenous administration. The primary endpoints evaluated for the *in vivo* pharmacokinetic studies (AUC0-tlast and MRT) demonstrated that PEGylation of human rFVIII increases the circulation time in comparison to Advate.

Administration of radiolabelled PEG-rFVIII to rats revealed extensive distribution of drug-derived radioactivity with maximum concentrations in mesenteric lymph nodes, plasma, blood, spleen, liver, adrenal glands, and kidneys. Radioactivity was also observed in the brain indicating that [3H]PEG-rFVIII-derived radioactivity crosses the blood:brain barrier at low levels. Elimination occurred primarily via urine, the half-life was between 24 and 30 days for male and female rats, respectively.

Toxicology

In both tested relevant species (rats and monkeys) no toxicity was observed for Adynovi even at the highest dose levels tested. Repeated doses of Adynovi resulted in the formation of anti-drug antibodies specific for

human FVIII or PEG and neutralising for FVIII activity in animal models. This effect is expected for a repeated administration of heterologous human protein drug to the animals.

Genotoxicity studies were not submitted in accordance with ICH S6(R1) Guideline "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals", stating that genotoxicity studies are not applicable to the assessment of safety of biotechnology - derived pharmaceuticals such as PEGylated recombinant Factor VIII.

Carcinogenicity studies were not submitted in accordance with ICH S6(R1) - Guidance for Industry. Preclinical Safety Evaluation of Biotechnology- derived Pharmaceuticals, stating that carcinogenicity testing of biological products is not required unless there is cause for concern.

No reproduction studies were submitted. This is considered acceptable as these studies would not be representative for the situation in humans due to the risk of incompatibility reactions based on an antigen-antibody reaction.

With regards to local tolerance, experimental observations of the *Cynomolgus* monkeys in the 4-week i.v. RDTS (study number 1933-018) revealed no findings of adverse local tolerance effects on the test animals. Microscopic findings at injection sites of rats and rabbits were comparable with controls and were consistent with a normal response expected after intravenous injection.

Ecotoxicity/environmental risk assessment

In accordance with the guideline CHMP/SWP/4447/00 (1), Adynovi as a protein is exempted from an environmental risk assessment since proteins are unlikely to result in a significant risk to the environment. Hence, Adynovi is not expected to pose a risk to the environment.

Immunogenicity

Based on the *in vitro* non-clinical immunogenicity assessment, Adynovi expresses a similar FVIII immunogenicity profile as Advate. Adynovi tested for its potential to induce cytokine release in an *in vitro* assay using human plasma and whole blood from healthy subjects, did not induce cytokine release. Results obtained in another comparative *in vitro* immunogenicity study, assessing the potential to induce complement activation, revealed that neither Adynovi nor Advate did activate the complement system in human plasma from healthy subjects *in vitro*.

Furthermore, Adynovi expresses a similar FVIII immunogenicity profile as ADVATE *in vivo*, in mice and monkeys. Adynovi induced anti-PEG antibodies only in mice that recognise FVIII as immunogenic foreign protein. This outcome indicates, that only patients who recognise FVIII as foreign protein may be at risk for developing antibodies against PEG after treatment with Adynovi.

PEG

A repeated administration with PEG2ru20KCOOH, a toxicological relevant unbound 20kD model PEG, was well tolerated in rats and did not show any signs of toxicity even at the highest dose tested. PEG size and clinical PEG doses applied with BAX 855 are in a range where occurrence of ependymal vacuolations is also not experienced so far with other pegylated compounds (CHMP Safety Working Party's response to the PDCO regarding the use of PEGylated drug products in the paediatric population, EMA/CHMP/SWP/647258/2012).

Even in the absence of PEG-related safety concerns identified within the non-clinical studies conducted by the Applicant, they are considered of too short duration for the assessment of safety, especially the potential for vacuolation in the choroid plexus, to support treatment with Adynovi beyond 4 weeks. However, it is acknowledged that studies of longer duration than 4 weeks with pegylated FVIII are not useful as those lack

clinical translatability due to species-specific antibody development, while a study with the unconjugated PEG part of Adynovi could theoretically be undertaken.

A 3-month repeated intravenous dose toxicity study of an unbound 20 kDa PEG from the public literature (Rudmann et al 2013) is considered to be of high quality and sufficient with respect to dose and duration. Although molecular weight is an important factor for the distribution and elimination of unconjugated PEG molecules, the influence of the polymer structure, which is not known, may also be important. However, no further evidence that the published data in Rudmann et al for linear 20 kDa PEG can be extrapolated to the branched 20 kDa PEG in Adynovi has been provided. The influence of the polymer structure on the pharmacokinetic and/or toxicological profile of unconjugated 20 kDa PEG molecules is still unknown. Hence, there remain uncertainties regarding the toxicological profile of Adynovi to support the use especially in the youngest age groups.

Assessment of paediatric data on non-clinical aspects

No data from juvenile animals were presented with regards to potential risks associated with long-term and chronic parenteral administration of Adynovi and potential long-term consequences of the PEG-moiety. Regarding the age of the animals in the 3-month repeated intravenous study of a linear 20 kDa PEG by Rudmann *et al*, the rats used were 49 days old at start, which corresponds to human adolescents.

On account of this, there remain uncertainties in relation to whether the younger children would be more vulnerable for potential PEG induced effects, including cell vacuolation, than adults. Due to the lack of a well-designed toxicology study of at least 3 month duration with the PEG molecule used in Adynovi (or a relevant surrogate) and appropriate data to support safe use in children, the use of Adynovi below the age of 12 is not supported from a nonclinical perspective.

2.3.6. Conclusion on the non-clinical aspects

The primary PD studies demonstrated a prolonged efficacy of the PEGylated rFVIII Adynovi in comparison to Advate *in vivo* and, therefore, support the clinical development and marketing authorisation of Adynovi.

In line with PD results, PK studies revealed a higher exposure to Adynovi in contrast to the non-PEGylated product providing a prolonged protective haemostatic effect.

Although no safety concerns arose from the toxicity studies performed, there remain uncertainties on potential long-term toxicological consequences of PEG accumulation, especially in juvenile individuals. A toxicological study of sufficient duration with the branched 20 kDa PEG in Adynovi was not provided. Further evidence for that the published data in Rudmann et al for linear 20 kDa PEG can be extrapolated to the branched 20 kDa PEG in Adynovi, was not provided either.

Although non-clinical toxicity data with young animals were presented, they did not cover the age range of the paediatric population below the age of 12.

Due to the limited knowledge in relation to whether the younger children would be more vulnerable for potential PEG induced effects, including cell vacuolation, than adults, an indication in children under 12 years is currently not supported by the non-clinical data.

2.4. Clinical aspects

2.4.1. Introduction

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- ***Tabular overview of clinical studies***

Study, Status	**Type of Study**	**Study Design**	**Primary Objective**	**Test Product(s), Dosage Regimen, Route of Administration**	**Number and Age of Subjects**	**Duration of Treatment**
Study 261101 **Complete** **CSR available**	Safety and PK	Phase 1, prospective, open label, cross-over, dose escalation	Assess the tolerability and safety of IV administration of Adynovi evaluated by clinical laboratory analyses, vital signs, adverse events and immunogenicity	**Adynovi and Advate IV bolus PK infusions:** 30 ±3 IU/kg OR 60 ±6 IU/kg	19 subjects 32(18-60) years	10 months
Study 261201 **Pivotal** **Complete** **CSR available**	Safety, Efficacy and PK	Phase 2/3, prospective, uncontrolled, two-arm, open label, multicenter study	to compare the ABR between prophylactic dosing regimen of Adynovi with on-demand treatment regimen	**Adynovi and Advate IV bolus PK infusions:** 45 ±5 IU/kg (subset of subjects in prophylaxis arm) **Adynovi IV bolus infusions:** <u>Fixed prophylaxis:</u> 45 ±5 IU/kg twice weekly OR <u>On-demand treatment:</u> 10 to 60 ±5 IU/kg	138 subjects 19 (12-58) years	18 months

Study 261302 Continuation ongoing	Safety, Efficacy and PK	Phase 3b, prospective, open label, multicenter study	Determine the 1. safety of Adynovi based on the incidence of FVIII inhibitory antibody development 2. the efficacy of Adynovi based on the ABR of spontaneous bleeding episodes	**Adynovi IV bolus infusion** Fixed prophylaxis: 1. Age ≥ 12 years: 45 ±5 IU/kg twice weekly 2. Age <12 years: 50 ±10 IU/kg twice weekly (may be increased up to 80 IU/kg) PK-tailored prophylaxis: based on individual PK to maintain a FVIII trough level ≥ 3%	~ 250 planned	~ 4 years
Study 261202 Paediatric Complete CSR available	Safety, Efficacy and PK	Phase 3, prospective, uncontrolled, open label, multicenter study	Assess the incidence of FVIII inhibitory antibodies	**Adynovi IV bolus infusion** Fixed prophylaxis: 50 ±10 IU/kg twice weekly **Adynovi and ADVATE IV bolus PK infusions:** 60 ±5 IU/kg (subset of subjects)	66 subjects 32 aged <6 years 34 aged 6 to 12 years	1 year
Study 261204 Surgery Ongoing Interim CSR available		Phase 3 prospective, uncontrolled, open-label, multicenter study	Evaluate the perioperative hemostatic efficacy of Adynovi in subjects undergoing major or minor elective or minor emergency surgical, dental or other invasive procedures	**Adynovi IV bolus infusion** Presurgical PK assessment, if applicable: 60 ±5 IU/kg Surgical dose and frequency: Major procedures: based on subject's PK to reach initial FVIII target levels of	~ 40 planned	~ 36 months

				80-100% Minor procedures: based on subject's IR to reach initial target FVIII levels of 30-60%		
Study 261203 **PUPs** **Ongoing**		Phase 3, prospective, multi-center, open label	Assess the incidence of FVIII inhibitory antibodies	**Adynovi IV bolus infusion** Prophylaxis initiated <3 years and <2 joint bleeds: 25-80 IU/kg at least once weekly On-Demand (if <3 years and <2 joint bleeds): IR: 50 ±5 IU/kg If FVIII inhibitor: 50 IU/kg 3 times weekly or up to 100-200 IU/kg daily, depending on SOC	~ 120 planned	
Study 261303 **PROPEL** **Ongoing**		Phase 3, prospective, randomized, multi-center clinical study	to compare 2 prophylactic dosing regimens targeting 2 different FVIII trough levels, by comparing the ABR	IV bolus infusion PK-guided to maintain FVIII target trough levels at: 1-3% with infusions approx. twice weekly OR approx. 10% (8-12%) with infusions every other day	~ 116 planned	

2.4.2. Pharmacokinetics

PK data are available from 3 completed studies (Study 261101, Study 261201 and Study 261202).

Analytical methods

Accuracy, precision, selectivity/specificity, stability and dilution capabilities of the chromogenic and the one-stage clotting assay could be demonstrated for measurement of FVIII activity of Adynovi, Advate and plasma FVIII in citrated, FVIII deficient plasma. Furthermore an appropriate validation of the ELISA used for determination of FVIII antigen in the plasma samples has been presented. The method principles as well as brief descriptions of the mentioned methods have been included in the provided validation documents.

In addition to the validation protocols, the Company has provided a study report which summarizes the outcome of a collaborative field study for evaluation and comparison of FVIII activity of recombinant FVIII products in hemophilic plasma. In particular, the assay results from laboratories using the one-stage clotting assay where compared with the results of laboratories using the chromogenic assay. The provided data indicate that for BAX 855

- both assays deliver more or less comparable results with respect to in-vitro recovery (101.0 - 124.3 for the one-stage clotting assay versus 95.4 -124.0 for the chromogenic assay) and
- the one-stage clotting assays shows a slightly better performance with respect to the intra- and inter-laboratory variance (%CV intra-lab 7.4 - 12.4 and inter-lab 14.7 - 17.5 for the one-stage clotting versus %CV intra lab 7.6 - 17.3 and inter-lab 10.1 -33.7 for the chromogenic assay).

Of note, this study is used by the Company to justify the one-stage clotting assay for release and potency labeling of drug product in the quality section (in contrast to the chromogenic assay which is the Ph. Eur. method foreseen for release control of recombinant FVIII products).

Furthermore, different aPTT reagents and their impact on assay variability have been investigated in the one-stage clotting assay for FVIII activity of BAX 855 in plasma samples. APTT reagents from different suppliers (ellagic acids/polyphenolic type or silica/kaolin) and different coagulation analysers (based on either optical or mechanical detection) were used for this study. The provided data indicate slightly higher values found with ellagic acid/polyphenolic type reagents as compared to silica/kaolin reagents whereas the type of analyser has no impact on the variability of the method. The measured Factor VIII activity for the pegylated factor VIII Adynovi in plasma samples is much more affected by the type of the used aPTT reagent as the initially submitted mean values would have indicated. For example the clotting assay gives results up to 165,2% respective 145,6% of the label claim when using C.K. Prest respective SynthaFax as aPTT reagent whereas when using APTT-SP as aPTT reagent in the one-stage clotting assay gives values of 67,2 respective 69,2% of the label for the lowest investigated concentration level of Adynovi.

PK Trial 261101

Study 261101 was a Phase 1, open-label, multicenter, cross-over, dose-escalation study designed to evaluate the safety and PK of single doses of Adynovi (30 and 60 IU/kg) in 8 adult male PTPs with severe haemophilia A (FVIII levels <1%) per dose level compared with corresponding single doses of Advate. This phase I trial was designed to determine the safety and PK properties of single intravenous doses of BAX 855 in patients with haemophilia A (factor VIII <1%) at two dose level cohorts, 30 U/kg and 60 U/kg. In addition, the PK properties of Advate were compared to those of Adynovi at the same dose level. The study demonstrated pharmacokinetic differences between Adynovi and Advate in adult haemophilia A patients. AUCinf was about 1.5- to 1.7-fold higher after administration of Adynovi, corresponding to a decrease in CL of about 30-50%, and t1/2 was about 1.4-fold longer than for Advate with the 1-stage clotting assay and 1.5-fold longer with the chromogenic assay. The estimated mean fold increase in MRT (mean residence time) of BAX 855 versus Advate was approximately 1.4.

Pivotal Trial 261201

Study 261201 was a multicenter, open-label, Phase 2/3 study to evaluate the safety, efficacy and PK of Adynovi administered as an IV injection in 137 adult or adolescent PTPs ≥12 years of age with severe haemophilia A. 26 subjects provided PK data at a dose of 45 IU/kg. The data from the phase 2/3 study 261201 demonstrated pharmacokinetic differences between Adynovi and Advate in adult and adolescent patients with haemophilia A. AUCinf was 2-fold and 1.8-fold higher in adults and adolescents, respectively, after administration of Adynovi, corresponding to a decrease in CL of about 35-40% as compared with Advate. Half-life was about 1.4-fold longer than for Advate in both age groups. The estimated mean fold increase in MRT (mean residence time) of Adynovi versus ADVATE was approximately 1.5.

Paediatric study 261202

Study 261202 was a multicenter, open-label, Phase 3 evaluation of the safety, PK, and efficacy of Adynovi for routine prophylaxis and control of bleeding in 66 PTPs <12 years of age with severe haemophilia A. 12 subjects provided PK data at a dose of 60 IU/kg. All subjects received twice weekly prophylactic treatment with 50 ± 10 IU/kg of BAX 855 over a period of 6 months or at least 50 exposure days (EDs), whichever occurred last. A subset of 31 subjects (14 and 17 in the younger and older age cohort, respectively) provided PK data. All evaluable subjects who participated in the PK portion of the study were to have 1 pre-infusion blood draw and 3 post-infusion blood draws. The latter were to be randomly selected from 3 choices for each blood draw. The IWRS was to manage the total numbers of subjects enrolled into each arm of the PK portion of the study, the time points of PK infusion and the post-infusion time points for blood draws. The objectives of this study were to determine the population PK of Adynovi and Advate in paediatric patients with severe haemophilia A and to identify sources of Adynovi and Advate exposure variability by covariate analysis.

Based on the present population pharmacokinetic analysis, half-life was shorter for Adynovi in children < 12 years than in adults and adolescents. In addition, IR was lower for children than for adult/adolescent patients. Accordingly, a somewhat higher prophylaxis dose is proposed for children, but at the same dosing interval as for adults/adolescents (40-60 IU/kg or up to 80 IU/kg twice weekly). The difference between the results from the 1-stage clotting assay and the chromogenic assay appeared to be somewhat greater in the paediatric population than in the adult/adolescent population.

Overview of PK parameters according to age groups

Table 8. Summary of pharmacokinetic parameters across age groups after a single dose of 50 ± 10 IU/kg of Adynovi or non-pegylated Advate, and the mean of individual ratios between Adynovi and Advate (studies 261201 and 261202).

Parameter	Age group	BAX 855	Advate	Mean ratio BAX/Advate[a)]
$T_{1/2}$ (h)	< 6 years [b)]	11.8	9.2	1.3
	6 to < 12 years [b)]	12.4	9.8	
	12 to < 18 years	13.4	9.4	1.4
	≥ 18 years	14.7	10.8	1.4
MRT (h)	< 6 years [b)]	17.0	13.3	1.3

Parameter	Age group	BAX 855	Advate	Mean ratio BAX/Advate[a)]
	6 to < 12 years [b)]	17.8	14.2	
	12 to < 18 years	18.0	11.6	1.5
	≥ 18 years	20.3	13.4	1.5
CL (mL/(kg·h))	< 6 years [c)]	3.1	4.2	NR
	6 to < 12 years [c)]	2.4	5.5	
	12 to < 18 years	3.9	6.1	0.67
	≥ 18 years	2.3	3.9	0.59
$AUC_{0-\infty}$ (IU•h/dL)	< 6 years [b)]	1950	1400	1.4
	6 to < 12 years [b)]	2010	1440	
	12 to < 18 years	1640	901	2.1
	≥ 18 years	2260	1290	1.8

a) not presented per age group in the paediatric study report

b) estimated by population PK approach

c) estimated by non-compartmental approach on sparse data

NR = not reported

Table 9. Mean (SD) Change in BAX 855 Incremental Recovery (IR) by Age Group (Studies 261101, 261201, 261202, 261204 and 261302, pharmacokinetic dataset)

Age Group	N	First IR (IU/dL:IU/kg)	Last IR (IU/dL:IU/kg)	Ratio of Last/First
<6 years	7	1.56 (0.141)	1.55 (0.309)	1.00 (0.226)
6 to <12 years	5	2.01 (0.366)	1.75 (0.444)	0.87 (0.146)
12 to <18 years	24	2.01 (0.514)	2.02 (0.736)	1.09 (0.666)
≥18 years	101	2.09 (0.410)	2.07 (0.497)	1.01 (0.265)

First IR = incremental recovery determined at Tmax after first dose.

Last IR = incremental recovery determined at Tmax after last dose

Abbreviations: IR, incremental recovery; N, number of subjects with 2 or more IRs; SD, standard deviation.

Table 10: Pharmacokinetic Parameters Using the One stage Clotting Assay (Arithmetic mean ± SD)

PK Parameters	Adynovi Adults (18 years and older) N = 18 Dose: 45 ± 5 IU/kg	Adynovi Adolescents (12-<18 years) N = 8 Dose: 45 ± 5 IU/kg
Design	Individual PK with Full Sampling[a]	
Terminal half--life [h]	14.69 ± 3.79	13.43 ± 4.05
MRT [h]	20.27 ± 5.23	17.96 ± 5.49
CL [mL/(kg·h)]	2.27 ± 0.84	2.73 ± 0.93
Incremental Recovery [(IU/dL)/(IU/kg)]	2.66 ± 0.68	2.12 ± 0.60
$AUC_{0\text{-}Inf}$ [IU·h/dL]	2264 ± 729	1642 ± 752
Vss [dL/kg]	0.43 ± 0.11	0.56 ± 0.18
Cmax [IU/dL]	122 ± 29	95 ± 25

- Abbreviations: C_{max}: maximum observed activity; AUC: area under the curve; MRT: mean residence time; CL: clearance; V_{ss}: body weight adjusted volume of distribution at steady-state,
- [a] Individual PK with 12 post-infusion samples.
- [b] Population PK model with 3 post-infusion samples based on randomized drawing schedule.
- [c] NA, Not applicable, as Incremental Recovery and C_{max} in children were determined by individual PK. Results for Incremental Recovery and C_{max} determined by individual PK in parenthesis.

Special populations

No studies to determine PK in patients with renal or hepatic impairment have been performed.

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials	0	0	0

Pharmacokinetic interaction studies

No pharmacokinetic interaction studies have been performed.

2.4.3. Pharmacodynamics

Primary pharmacodynamics, safety pharmacology and PK properties of the pegylated product were demonstrated in nonclinical studies.

2.4.4. Discussion on clinical pharmacology

The Applicant has explored the PK parameters of Adynovi in 16 adults in PK trial 261101 comparatively to Advate, which is the non-pegylated parent molecule of Adynovi. Data from 8 subjects at the 30 IU and 8 subjects at the 60 IU dose level are available. In addition, PK data are available from 25 subjects enrolled in the pivotal trial 261201 at a dose level of 45± 5 IU in comparison to the same dose of Advate. The PK exercise for Adynovi was repeated after 6 months of prophylactic treatment.

The PK properties of Adynovi in children have been investigated using a nonlinear mixed effects model approach in trial 261202 in 31 subjects, 14 aged <6 and 17 aged 6 to <12 years. In addition, point estimates for summary PK parameters were derived by the non-compartmental estimation approach.

The provided PK parameters, among which AUC, IR, t1/2, MRT and clearance are the most important, are in line with guideline requirements and therefore endorsed. The numbers of subjects in the different age groups exceed the requirements of the current valid guideline EMA/CHMP/BPWP/144533/2009 rev. 1. In all trials, a direct comparison of PK parameters of Adynovi with its unpegylated parent molecule, Advate, has been provided.

It is apparent that a modest prolongation of half-life and a greater exposure compared to the unpegylated parent molecule can be achieved in adults and adolescents. As expected, the youngest age cohort showed a faster turnover than the older age cohorts. Results obtained with the one-stage clotting assay and the chromogenic assay are similar.

The current pharmacokinetic data indicate that Adynovi CL adjusted for bodyweight decreases with age. There was no relevant difference in half-life between younger paediatric patients (< 6 years) and older paediatric patients (6 to < 12 years). However, the half-life in children <6 years of age may be shorter and this should be taken into account when monitoring patients and determining individual dose and dosing interval.

Nevertheless, based on the average doses given to these two age cohorts and efficacy data in terms of bleeding episodes in the paediatric efficacy study, the Applicant suggests that the previously proposed starting dose interval of 40-60 IU/kg in paediatric patients is relevant. It can be agreed that available data on dose adjustments and incidences of bleedings do not indicate a need for a recommendation for an adjusted starting dose in children. It should also be taken into account that considerable variability in individual PK characteristics is expected and that individual dose adjustments often have to be made based also on individual bleeding tendency. Thus, based on currently available data, the response regarding starting dose recommendations can be accepted.

The repeat PK evaluation after continuous treatment for 6 months, which was done in the pivotal trial 261201, shows similar PK parameters and thus satisfies the guideline requirement of demonstrating no decrease in FVIII activity after prolonged use.

Data from the pharmacokinetic subset in study 261201 indicated that annualised bleeding rate (ABR) increased with decreased half-life of Adynovi. These data might suggest that the individual dose adjustment based on IR at Cmax was not sufficient to obtain adequate efficacy in patients with a short Adynovi half-life, as data obtained at Cmax cannot be used to estimate half-life. Patients with a short half-life might possibly need a shorter dosing interval rather than a higher dose. The Applicant should discuss whether the same trend, i.e. increased ABR with decreasing product half-life, has been observed for other FVIII products or whether this is a specific problem for Adynovi, i.e. whether variability in half-life is greater for Adynovi than for other products. In the latter case, it should be discussed how patients with short Adynovi half-life should be identified and handled in clinical praxis. The Applicant responded that half-life for FVIII products is highly variable and that differences in half-life are reflected in differences in time for FVIII levels to fall below 1%. However, dose adjustments are generally not

based on trough levels of activity but on IR at FVIII Cmax, which does not reflect half-life. This problem has been recognised previously for unpegylated FVIII, e.g. in the article by Collins et al (2011) cited by the Applicant in the response. The authors referred to simulations demonstrating that the trough level and time per week with FVIII less than 1 IU/dL are affected more by half-life and frequency of infusions and less by recovery (IR) and dose/kg. Thus, this problem appears to be general for FVIII and not specific for the pegylated FVIII.

As the PD effects of FVIII as a major player in the coagulation cascade are clear to demonstrate pharmacodynamics in nonclinical studies only is considered acceptable.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology programme supports the application for Adynovi by elucidating the pharmacokinetic properties of this modified FVIII product.

2.5. Clinical efficacy

2.5.1. Dose response studies and main clinical studies

STUDY 261201

This was a Phase 2/3, Multi-center, Open Label Study of Efficacy, Safety, and Pharmacokinetics of PEGylated Recombinant Factor VIII (Adynovi) Administered for Prophylaxis and Treatment of Bleeding in Previously Treated Patients with Severe Haemophilia A (FVIII activity <1%).

Study Participants

Inclusion Criteria

The main criteria for inclusion were: a diagnosis of severe haemophilia A, previous treatment with FVIII concentrates for at least 150 EDs, and that the subject be male and aged 12-65 years at screening.

Exclusion Criteria

The main criteria for exclusion were the presence of detectable FVIII inhibitory antibodies (≥ 0.4 BU using the Nijmegen modification of the Bethesda assay), history of FVIII inhibitory antibodies, diagnosis of an inherited or acquired defect other than haemophilia A, or that the subject had recently used another pegylated drug.

Treatments

Subjects were enrolled to receive either prophylactic treatment with Adynovi at a dose of 45 ± 5 IU/kg twice weekly (Arm A) for ≥50 EDs or 6 months ±2 weeks, whichever occurred last, or on-demand therapy with Adynovi at a dose of 10 to 60 IU/kg dose (Arm B) for an approximate duration of 6 months.

Subjects meeting any of the following criteria during prophylaxis may have had their Adynovi dose increased from 45 ± 5 IU/kg to 60 IU/kg:

• Two or more spontaneous (not related to trauma) bleeding episodes in the same target joint within any 2-month period, or

• One or more spontaneous (not related to trauma) bleeding episodes in a non-target joint within any 2-month period or

• FVIII trough level < 1% and the investigator assesses the study subject was at increased risk of bleeding.

Figure 1 Adynovi and ADVATE Treatment Guidelines for Bleeding Episodes

BAX 855 and ADVATE Treatment Guidelines for Bleeding Episodes		
Type of Bleeding Episode	**FVIII Level Required (%)** ***Dose***	**Frequency of Dosing**
Minor (corresponds with mild severity) Early hemarthrosis, mild muscle bleeding, or mild oral bleeding, including, epistaxis	20 to 40 % *Dose* *10 to 20 ± 5 IU/kg*	Repeat infusions every 12 to 24 hours. Duration: at least 1 day, until the bleeding episode is resolved or healing is achieved

BAX 855 and ADVATE Treatment Guidelines for Bleeding Episodes		
Type of Bleeding Episode	**FVIII Level Required (%)** ***Dose***	**Frequency of Dosing**
Moderate (corresponds with moderate severity) Moderate bleeding into muscles, bleeding into the oral cavity, definite/ more extensive hemarthroses, and known trauma	30 to 60% *Dose* *15 to 30 ± 5 IU/kg*	Repeat infusions every 12 to 24 hours for 3 days or more until the pain and acute disability/incapacity are resolved
Major/life-threatening (corresponds with severe/life or limb threatening severity) Significant gastrointestinal bleeding, intracranial, intra-abdominal, or intrathoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces or iliopsoas sheath, fractures, head trauma	60 to 100% *Dose* *30 to 60 ± 5 IU/kg* In case of life-threatening bleeding episodes a dose of 80 ± 5 IU/kg may be considered.	Repeat infusions every 8 to 12 hours until the bleeding episode/threat is resolved

The required units were to be calculated according to the following formula:

body weight (kg) x desired FVIII rise (% or IU/dL) x {reciprocal of observed recovery}

Subjects meeting any of the following criteria during prophylaxis may have had their Adynovi dose increased from 45 ± 5 IU/kg to 60 IU/kg:

• Two or more spontaneous (not related to trauma) bleeding episodes in the same target joint within any 2-month period, or

• One or more spontaneous (not related to trauma) bleeding episodes in a non-target joint within any 2-month period or

• FVIII trough level < 1% and the investigator assesses the study subject was at increased risk of bleeding.

Objectives

The primary objective was to compare the annualized rates of bleeding episodes (ABR) between subjects who received a prophylactic dosing regimen of Adynovi with those who received an on-demand treatment regimen.

The key secondary objective was to estimate the rate of success of Adynovi for treatment of bleeding episodes.

Other secondary efficacy objectives included:

- To characterize Adynovi for treatment of bleeding episodes through the number of Adynovi infusions needed for the treatment of a bleeding episode and through the length of intervals between bleeding episodes
- To compare the total weight-adjusted consumption of Adynovi for each regimen

Outcomes / endpoints

The primary outcome measure was annualized bleeding episode rate (ABR).

Secondary Outcome Measures:

- Rate of success of Adynovi for treatment of bleeding episodes
- Number of Adynovi infusions used for the treatment of bleeding episodes
- Time intervals between bleeding episodes
- Weight-adjusted consumption of Adynovi

The subject was to rate the severity of the bleeding episode as mild, moderate or severe and was to rate his overall response for each bleeding episode 24 (± 2) hours after initiating treatment using a 4-point Efficacy Rating Scale. Efficacy was defined as a response of good or excellent. An inadequate response to Adynovi treatment was defined as a rating of fair or none 24 (± 2) hours after initiation of Adynovi infusion. Since the efficacy rating was based to a large degree on cessation of pain, the investigator/subject was to consider the injury-related symptoms when performing the efficacy rating 24 hours after initiating treatment, particularly in the case of injury-related bleeding into one or more than one location.

Figure 2 Efficacy Rating scale for treatment of bleeding episodes

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

Sample size

132 subjects were to be assigned to Arm A (prophylactic treatment, N=115) or Arm B (on-demand treatment, N=17). Assuming a dropout rate of 10% following study arm assignment, approximately 119 subjects were expected to be evaluable for efficacy: approximately 104 subjects from Arm A and 15 subjects from Arm B.

Primary efficacy outcome measure: In the Advate prophylaxis study the mean ABR in the on-demand arm was 48.9, the range of ABRs extended from 13.0 to 120.5. To be confident that the sample size would not be underestimated, a mean of 27.5 was assumed. The mean ABR in any prophylactic arm was 3.8. These results were used in the sample size evaluation of the current study. Under these assumptions the probability that prophylaxis would be successful (see below) was approximately 82.6%.

Success (in treatment of bleeds) was defined as a rating of excellent or good. Assuming a true success rate of a subject to be Gaussian distributed with mean 80% and standard deviation 12% and assuming the same bleed rate as for the primary endpoint, the power (comparing to a threshold of 70%) was estimated as 87.3%.

With a sample size of 104 evaluable subjects with ≥ 50 EDs in Arm A, and with 2 subjects developing inhibitory antibodies, the upper limit of the 95% CI (Clopper-Pearson) of the proportion of subjects developing inhibitory antibodies should not have exceeded 6.8%.

Randomisation

Subjects were assigned to a treatment arm based upon their pre-study FVIII treatment regimen; however, once 17 subjects were assigned to the on-demand arm, subsequent subjects who had previously received on-demand treatment were assigned to prophylaxis.

Blinding (masking)

This was a non-randomized, open-label, treatment regimen comparison clinical study.

Statistical methods

Analysis Sets

The Full Analysis Set (FAS) comprised all subjects who were assigned to the prophylactic arm or the on-demand treatment regimen.

The Per Protocol Analysis Set (PPAS) comprised all subjects who were assigned to the prophylactic or the on-demand treatment regimen, treated with their originally assigned dose for the entire duration of study participation and who fulfilled the compliance requirements.

The Safety Analysis Set (SAS) comprised all subjects treated with at least 1 Adynovi dose. All safety analyses for Adynovi were to be performed on the SAS.

Statistical Analysis of Haemostatic Efficacy Endpoints

The primary objective was to compare the annualised rates of bleeding episodes (ABR) between subjects who received a prophylactic dosing regimen of Adynovi with those who received an on-demand treatment regimen, the on-demand arm was considered as the treatment regimen control group for efficacy of prophylaxis. The key secondary objective was to estimate the rate of success of Adynovi for treatment of bleeding episodes.

Primary Outcome Measure

Comparisons between prophylactic and on-demand treatment were based on ABR estimates from a negative binomial regression model (with a logarithmic link function), taking into account the fixed effect of regimen (prophylaxis vs on-demand), presence or absence of target joints at screening, age at screening as a continuous covariate, and the duration of the OPE as an offset. Ratios of treatment means (point estimates and their 95% CIs) were estimated within this model. Prophylactic treatment was considered successful if the upper limit of the 95% CI for the ratio between treatment regimen did not exceed 0.5 (corresponding to a 50% reduction of the mean ABR compared to the on-demand treatment).

The following null hypothesis was tested against the one-sided alternative hypothesis at the 2.5% level of statistical significance:

$H01: \mu1=0.5*\mu2$, $Ha1: \mu1<0.5*\mu2$

where μ1 and μ2 were the mean ABRs in on prophylaxis and on-demand, respectively.

The logarithm of expectation of bleeds per observation time in years (and their 95% CIs) was back-transformed to the original scale by exponentiation, resulting in ratios (95% CIs for ratios) of mean ABRs. In addition, sensitivity analyses were performed using alternative model: without adjustments, adjusted for Stratum, adjusted for Stratum and Age Category.

Key Secondary Outcome Measure

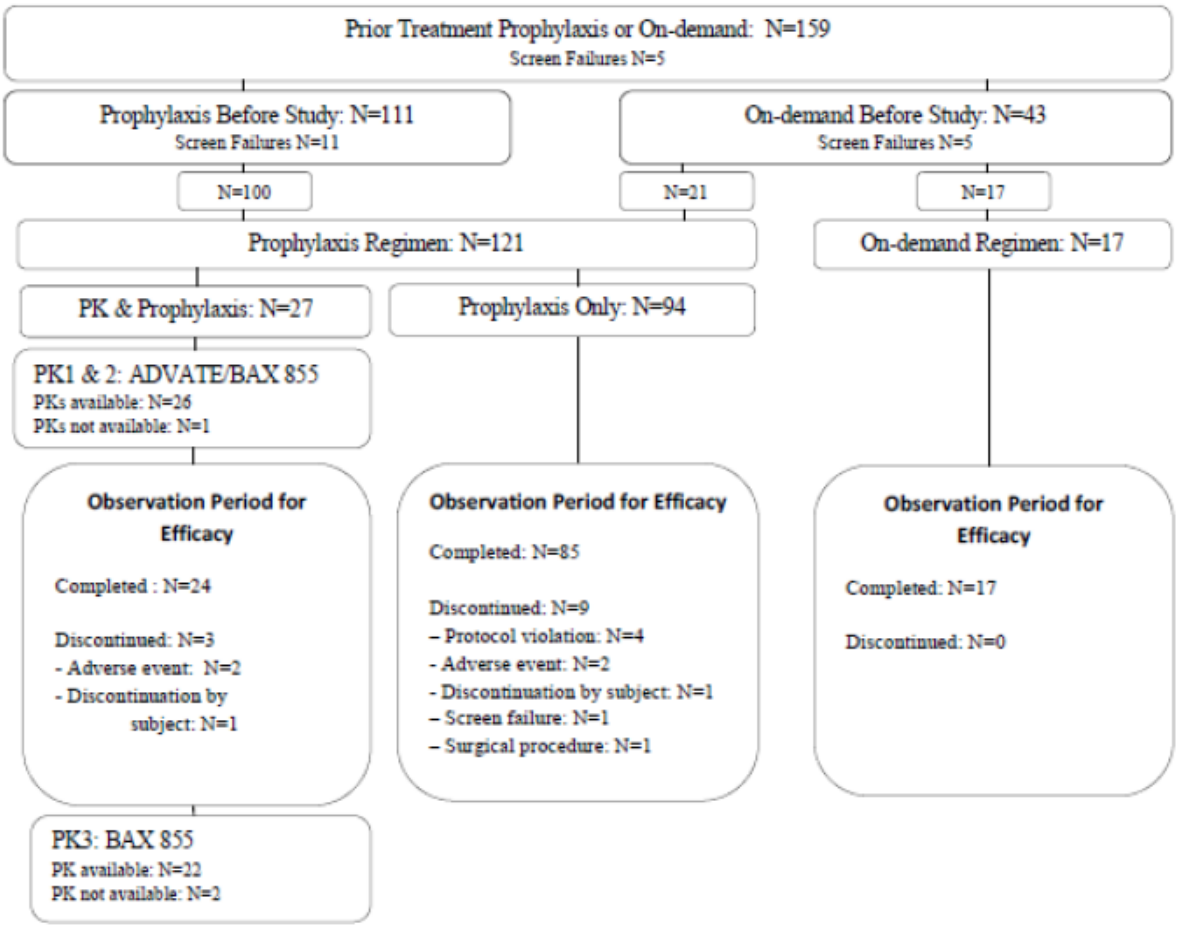
Success in the control of bleeding was defined as a rating of excellent or good using the Efficacy Rating Scale for Treatment of Bleeding Episodes measured 24 hours after initiation of treatment for the bleeding episode. Success proportion (95% CI) was estimated within a general estimating equation (GEE) model framework. The model accounted for the fixed effects of on-demand vs. prophylactic regimen, bleed type (joint bleed vs non-joint bleed) and severity, and a random subject effect. For the dependent variable (success: yes/no) a binomial distribution and a log link was to be assumed, and for the subject effect (defined by a repeated statement) an independence working correlation structure was used to start the estimation. Estimated model parameter values and CI limits were back-transformed to the original scale by exponentiation.

The lower limit of the 95% CI was compared to the threshold of 70% (implicitly testing the null hypothesis of success rate=70% versus the one-sided alternative of success rate >70% at the 2.5% level of statistical significance).

Results

Participant flow

Figure 3 Patient disposition flowchart – Study 261201



Recruitment

Initiation: First Subject In (FSI): January 31, 2013

Study Completion: Last Subject Out (LSO): July 17, 2014

Duration Approximately 18 months from FSI to LSO

Eighty-six (86) study sites in Europe, the US, Australia and Asia participated in this study; 72 study sites enrolled subjects and 14 sites were initiated but were inactive.

Conduct of the study

There were 4 protocol amendments to the Protocol version 2012 OCT 19. The amendments were implemented prior to analysis.

Changes in some of the Protocol Amendments did not affect all assessments. Introduction of the longer 84 to 96 hour washout prior to PK-3 analysis was introduced in Protocol Amendments 3 and 4, which were implemented after the majority of subjects completed the month 3 visit. Based on Protocol Amendment 1, IR was only to be assessed for subjects in the prophylactic arm of the study and only at visit Week 2 and Month 3, so many subjects do not have IR assessments. This was modified in Amendment 3 and Amendment 4 so that additional IR at each study visit was optional and could have been performed also on subjects in the on-demand arm. These changes did not impact the primary outcome measure (ABR).

Of 1181 protocol deviations reported in the SAS during the study, 41 (3.5%) were major, 1140 (96.5%) were minor. An individual assessment of each protocol deviation indicated that none had any impact upon the conduct of the study or the safety and efficacy outcomes.

The 41 major protocol deviations included:

• 1 for eligibility: Subject 252006 was assigned to the prophylactic arm, but treated himself only on-demand, and thus, he was discontinued.

• 18 for IP administration, including: 7 cases of an incorrect prophylactic dose being admininstered (usually higher), 5 cases of the wrong treatment being administered (e.g. ADVATE rather than Adynovi), 4 cases of incorrectly stored product being administered, 1 case of a subject not receiving 50 EDs before the end of treatment, and 1 case of a subject who was treated on-demand before the study being assigned to the prophylactic arm before the on-demand filled-up.

• 10 for protocol schedule, including: 6 cases of missed study visits, 2 cases of procedures being performed before the ICF was signed because the procedures were to be included in the next protocol amendment, 1 case of a PK assessment being performed without adequate washout, and 1 case of the repeat PK being done before at least 50 EDs. In addition, there was 1 case of procedures being performed before eligibility was confirmed, in a subject who was not treated with Adynovi.

• 6 for procedures not being done.

• 6 for other reasons, including: 4 for procedures done before the ICF was signed because the procedures were to be included in the next protocol amendment and 2 for subjects not receiving ≥ 50 EDs of prophylactic treatment.

Baseline data

Table 15 Age of Subjects in Treatment Arm- FAS- Study 261201

Mean (SD) and Median (Min ; Max) Age in Years of Subjects by Treatment Arm in FAS						
Subgroup	**Total**		**Prophylaxis**		**On-Demand**	
All	30.0 (12.34) 29.0 (12 ; 58)	N=138	29.8 (12.53) 28.0 (12 ; 58)	N=121	31.5 (11.05) 32.0 (13 ; 56)	N=17
12 to < 18 years	14.5 (1.58) 15.0 (12 ; 17)	N=25	14.5 (1.53) 15.0 (12 ; 17)	N=23	15.0 (NA) NA (13 ; 17)	N=2
18 to 65 years	33.4 (10.96) 31.0 (18 ; 58)	N=113	33.4 (11.18) 30.0 (18 ; 58)	N=98	33.7 (9.7) 32.0 (19 ; 56)	N=15
Source: Table 3.						

Table 11 Race and Ethnicity of Subjects in Treatment Arm- FAS- Study 261201

Race and Ethnicity of Subjects by Treatment Arm in FAS		
	Prophylaxis (N=121) n (%)	**On-Demand (N=17)** n (%)
Race		
Asian	27 (22.3%)	6 (35.3%)
Black or African American	1 (0.8%)	0 (0%)
White	93 (76.9%)	11 (64.7%)
Other	0 (0.0%)	0 (0.0%)
Ethnicity		
Hispanic or Latino	6 (5.0%)	0 (0%)
Not Hispanic or Latino	115 (95.0%)	17 (100.0%)
Source: Table 4.		

Table 13 Proportion of Subjects with target joints at screening - FAS- Study 261201

Proportion of Subjects with Target Joints at Screening in FAS		
Target Joints at Screening	Prophylaxis (N=121) n (%)	On-Demand (N=17) n (%)
0	42 (34.7%)	2 (11.8%)
1	24 (19.8%)	4 (23.5%)
2	22 (18.2%)	5 (29.4%)
3	16 (13.2%)	3 (17.6%)
4	9 (7.4%)	2 (11.8%)
5	6 (5.0%)	0 (0%)
6	2 (1.7%)	1 (5.9%)
Source: Table 4.		

Table 14 of HIV or HCV infections in subjects -Study 261201

Subjects with HCV or HIV Infections		
Treatment Regimen	HCV (N=138)	HIV (N=138)
Prophylaxis	65 (53.7%)	16 (13.2%)
On-demand	12 (70.6%)	2 (11.8%)
Source: Table 4.		

The majority of subjects (84/137) did not know their hemophilia gene mutation. Among those who knew their gene mutation, the most common (29/137) were inversion of intron 22 mutations. The majority of subjects (73/137) reported no family history of hemophilia. In the case of a positive family history, 34/137 subjects had an affected brother, followed by an uncle (15/137) and grandfather (7/137).

Approximately half of subjects had previously received vaccinations against HAV (41.6 %) and HBV (59.1 %), and 16.1% of subjects had a history of treatment with pegylated medication, which in all cases was the use of pegylated interferon for the treatment of hepatitis C or Adynovi for participation in the phase 1 study 261101.

Numbers analysed

The numbers of subjects in each analysis set were:

- 138 subjects: Full analysis set (FAS)
- 118 subjects: Per-protocol analysis set (PPAS)
- 137 subjects: Safety analysis set (SAS) for Adynovi
- 151 subjects: ADVATE safety analysis set (ASAS)
- 26 subjects: Pharmacokinetic full analysis set (PKFAS)

The FAS comprised all subjects who were assigned to either arm of the study (ie, prophylaxis or on-demand), and the SAS included all subjects treated with at least 1 infusion of Adynovi (the ASAS included all subjects treated with at least 1 infusion of ADVATE). There were no subjects included in the SAS but excluded from the FAS (Listing 53 [appendix: Patients Excluded from Efficacy Analysis]). One subject (483001) was assigned to prophylactic treatment with Adynovi (in the FAS), but was not treated with Adynovi, and thus was not in the SAS.

Outcomes and estimation

Table 15 Annualized Bleeding Rate Primary Analysis in Age Subgroups –FAS- Study 261201

ABR Primary Analyses with Age Subgroups in FAS					
	Statistics[a]	**Prophylaxis**	**On-Demand**	**Ratio Prophylaxis/On-Demand**	**One-sided p-value**
All Ages	N	120	17	NA	
	Mean (95% CI)	4.3 (3.4 ; 5.5)	43.4 (25.2 ; 74.8)	0.10 (0.06 ; 0.19)	p <0.0001
Subgroup: 12 to <18 Years	N	23	2	NA	
	Mean (95% CI)	5.0 (3.2 ; 7.7)	39.9 (11.5 ; 138.8)	0.17 (0.04 ; 0.68)	p =0.0630
Subgroup: 18 to 65 Years	N	97	15	NA	
	Mean (95% CI)	4.1 (3.1 ; 5.5)	43.9 (23.9 ; 80.8)	0.10 (0.05 ; 0.19)	p <0.0001
[a] Point estimates for the mean with 95% CI from negative binomial regression model Source: Table 18, Table 20.					

Comparisons between prophylactic and on-demand treatment were based on ABR estimates from a negative binomial regression model, taking into account the treatment regimen, target joints and age at screening, and duration of the OPE. The primary outcome analysis of ABRs was performed on the FAS, and the analysis performed on the PPAS confirmed and supported the result of the FAS for the primary outcome.

ABR Descriptive Analyses

ABR by Target Joint Status, Bleeding Site and Cause

Analysis for the PPAS: ABR results are presented by target joint status at screening, bleeding site and cause

Mean joint ABRs were lower for those without target joints at screening compared with those with target joints at screening, although median joint ABRs were similar for those without and with arthropathy screening. However, there were only 2 subjects in the on-demand arm without target joints at screening, and thus, a comparison between those without and with target joints is limited.

Table 16 Annualized Bleeding Rate by bleeding site and Cause for each treatment arm in PPAS-Study 261201

ABRs by Bleeding Site and Cause for Each Treatment Arm in PPAS			
Category	**Statistic**	**Prophylaxis N=101**	**On-Demand N=17**
All Sites/Causes	Mean (SD)	3.7 (4.7)	40.8 (16.3)
	Median (Q1 ; Q3)	1.9 (0.0 ;5.8)	41.5(31.7;51.1)
Site: Joint	Mean (SD)	1.8 (3.0)	34.7 (15.1)
	Median (Q1 ; Q3)	0.0 (0.0 ;2.0)	38.1 (24.5; 44.6)
Site: Non-Joint	Mean (SD)	1.8 (3.2)	6.1 (6.7)
	Median (Q1 ; Q3)	0.0 (0.0; 2.1)	3.7 (2.1; 9.3)
Cause: Spontaneous/Unknown	Mean (SD)	2.1 (3.5)	26.0 (19.6)
	Median (Q1 ; Q3)	0.0 (0.0 ;2.2)	21.6(11.2;33.2)
Cause: Injury	Mean (SD)	1.6 (2.6)	14.9 (15.3)
	Median (Q1 ; Q3)	0.0 (0.0; 2.0)	9.3 (0.0; 25.5)

Forty out of 101 subjects (40%) experienced no bleeding episodes, 58 out of 101 subjects (57%) experienced no joint bleeding episodes, and 58 out of 101 subjects (57%) experienced no spontaneous bleeding episodes in the prophylaxis arm. All subjects in the on-demand arm experienced a bleeding episode, including a joint or spontaneous bleeding episode.

A total of 518 bleeding episodes were treated with Adynovi in the per protocol population. Of these, 361 bleeding episodes (n=17 subjects) occurred in the on demand arm and 157 (n=61 subjects) occurred in the prophylaxis arm. The median dose per infusion to treat all bleeding episodes in the per protocol population was 32.0 (Interquartile Range (IQR): 21.5) IU per kg. Overall, 95.9% of bleeding episodes were controlled with 1 to 2 infusions and 85.5% were controlled with only 1 infusion. Of the 518 bleeding episodes, 96.1% were rated excellent (full relief of pain and cessation of objective signs of bleeding after a single infusion) or good (definite pain relief and/or improvement in signs of bleeding after a single infusion) in their response to treatment with Adynovi.

Table 17 Efficacy Rating scale for Treatment of bleeding episodes by age group –FAS- Study 261201

Table 22
Efficacy Rating Scale for Treatment of Bleeding Episodes: Ratings of Excellent/Good by Age Group
(Study 261201: Full Analysis Set)

Parameter	Statistics	Result
Age Group = All		
Proportion of Bleeds with rating of excellent/good[a]	N	81
	Point Estimate for Proportion	0.96
	95% CI for Proportion	0.91 ; 0.98
Hypothesis[b] Test	One-sided p-value	<.0001
Age Group = 12 to <18 years		
Proportion of Bleeds with rating of excellent/good[a]	N	17
	Point Estimate for Proportion	0.97
	95% CI for Proportion	0.89 ; 0.99
Hypothesis[b] Test	One-sided p-value	0.0001
Age Group = 18 to 65 years		
Proportion of Bleeds with rating of excellent/good[a]	N	64
	Point Estimate for Proportion	0.96
	95% CI for Proportion	0.90 ; 0.99
Hypothesis[b] Test	One-sided p-value	<.0001

[a] Includes all bleeding episodes treated with BAX 855 in subjects on on-demand and prophylaxis treatment regimens
[b] H_0: $\pi \leq 0.7$ H_a: $\pi > 0.7$ where π is the proportion of ratings of excellent/good

Bleeding episodes were characterized by site (joint, non-joint, or unknown), cause (spontaneous/unknown or injury), severity (mild, moderate, or severe, and treatment regimen (prophylaxis or on-demand). The haemostatic efficacy of Adynovi for the treatment of bleeding episodes was assessed by the number of infusions to treat a bleeding episode, hemostatic efficacy rating, and the total dose administered to treat a bleeding episode.

Table 18 Characteristics of bleeding episodes treated with Adynovi by age group –FAS- Study 261201

Table 26
Characteristics of All Bleeding Episodes Treated with BAX 855 by Bleeding Site and Cause by Age Group (Study 261201: Full Analysis Set)

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

Table 19 Characteristics of all bleeding episodes treated with Adynovi by bleeding severity and age group –FAS- Study 261201

Table 27
Characteristics of All Bleeding Episodes Treated with BAX 855 by Bleeding Severity by Age Group (Study 261201: Full Analysis Set)

Treatment Regimen	Parameter	Category/ Statistics	Units	Severity of Bleeding Episode			All
				Minor N=272 n (%)	Moderate N=282 n (%)	Severe N=37 n (%)	N=591 n (%)
Age Group = All							
Prophylaxis	# of infusions per bleed	1	Bleeds	82 (92.1)	98 (76.0)	7 (58.3)	187 (81.3)
		2	Bleeds	6 (6.7)	21 (16.3)	4 (33.3)	31 (13.5)
		3	Bleeds	1 (1.1)	7 (5.4)	1 (8.3)	9 (3.9)
		≥4	Bleeds	0 (0.0)	3 (2.3)	0 (0.0)	3 (1.3)
	Hemostatic Efficacy at resolution of bleed	Excellent	Bleeds	49 (55.1)	36 (27.9)	0 (0.0)	85 (37.0)
		Good	Bleeds	36 (40.4)	85 (65.9)	8 (66.7)	129 (56.1)
		Fair	Bleeds	1 (1.1)	6 (4.7)	1 (8.3)	8 (3.5)
		None	Bleeds	0 (0.0)	2 (1.6)	3 (25.0)	5 (2.2)
		Not Reported	Bleeds	3 (3.4)	0 (0.0)	0 (0.0)	3 (1.3)
	Total dose per bleed [IU/kg]	N	Bleeds	89	129	12	230
		Mean (Std)	IU	35.5 (15.5)	48.0 (34.7)	63.5 (28.9)	43.9 (29.4)
		Median	IU	37.6	42.2	46.5	39.6
		Q1 ; Q3	IU	21.8 ; 44.5	25.2 ; 50.6	43.7 ; 92.6	24.2 ; 47.9
		Min ; Max	IU	11.5 ; 92.6	8.4 ; 257.1	25.3 ; 113.7	8.4 ; 257.1
On-Demand	# of infusions per bleed	1	Bleeds	182 (99.5)	121 (79.1)	15 (60.0)	318 (88.1)
		2	Bleeds	1 (0.5)	27 (17.6)	5 (20.0)	33 (9.1)
		3	Bleeds	0 (0.0)	3 (2.0)	3 (12.0)	6 (1.7)
		≥4	Bleeds	0 (0.0)	2 (1.3)	2 (8.0)	4 (1.1)

Table 27
Characteristics of All Bleeding Episodes Treated with BAX 855 by Bleeding Severity by Age Group (Study 261201: Full Analysis Set)

	Hemostatic Efficacy at resolution of bleed	Excellent	Bleeds	84 (45.9)	61 (39.9)	6 (24.0)	151 (41.8)
		Good	Bleeds	99 (54.1)	86 (56.2)	13 (52.0)	198 (54.8)
		Fair	Bleeds	0 (0.0)	6 (3.9)	4 (16.0)	10 (2.8)
		None	Bleeds	0 (0.0)	0 (0.0)	2 (8.0)	2 (0.6)
		Not Reported	Bleeds	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total dose per bleed [IU/kg]	N	Bleeds	183	153	25	361
		Mean (Std)	IU	25.4 (10.4)	37.8 (20.4)	64.4 (73.9)	33.3 (26.5)
		Median	IU	25.3	30.9	43.2	26.4
		Q1 ; Q3	IU	15.7 ; 30.9	22.7 ; 49.2	36.3 ; 66.8	19.2 ; 40.8
		Min ; Max	IU	6.8 ; 48.8	12.0 ; 128.9	19.8 ; 400.0	6.8 ; 400.0
Total	# of infusions per bleed	1	Bleeds	264 (97.1)	219 (77.7)	22 (59.5)	505 (85.4)
		2	Bleeds	7 (2.6)	48 (17.0)	9 (24.3)	64 (10.8)
		3	Bleeds	1 (0.4)	10 (3.5)	4 (10.8)	15 (2.5)
		≥4	Bleeds	0 (0.0)	5 (1.8)	2 (5.4)	7 (1.2)
	Hemostatic Efficacy at resolution of bleed	Excellent	Bleeds	133 (48.9)	97 (34.4)	6 (16.2)	236 (39.9)
		Good	Bleeds	135 (49.6)	171 (60.6)	21 (56.8)	327 (55.3)
		Fair	Bleeds	1 (0.4)	12 (4.3)	5 (13.5)	18 (3.0)
		None	Bleeds	0 (0.0)	2 (0.7)	5 (13.5)	7 (1.2)
		Not Reported	Bleeds	3 (1.1)	0 (0.0)	0 (0.0)	3 (0.5)
	Total dose per bleed [IU/kg]	N	Bleeds	272	282	37	591
		Mean (Std)	IU	28.7 (13.2)	42.4 (28.3)	64.1 (62.4)	37.5 (28.1)
		Median	IU	25.8	37.9	45.3	30.9
		Q1 ; Q3	IU	16.9 ; 38.5	22.9 ; 49.4	36.4 ; 73.3	21.2 ; 45.3

Table 20 bleeding Episode Rate per infusion by Time from last prophylactic infusion –FAS- Study 261201

Bleeding Episode Rate per Infusion by Time from Last Prophylactic Infusion in the FAS					
	Time Since Last Prophylactic Infusion				
Cause	≤24 h	>24 to ≤48 h	>48 to ≤72 h	>72 to ≤96 h	>96 h
All	0.0080	0.0119	0.0125	0.0079	0.0291
Spontaneous/Unknown	0.0044	0.0068	0.0073	0.0058	0.0179
Injury	0.0036	0.0051	0.0052	0.0021	0.0112

Table 21 Consumption of Adynovi - FAS- Study 261201

Table 31
Consumption of BAX 855 (Study 261201: Full Analysis Set)

Consumption of BAX 855	Units	N	Mean (SD)	Min	Q1	Median	Q3	Max
Per Prophylactic Infusion [IU/kg]	Infusion	5941	44.51 (4.556)	8.4	42.56	44.59	46.75	69.0
Per PK Infusion [IU/kg]	Infusion	50	45.48 (2.592)	38.9	44.19	45.70	47.02	54.8
Per Treatment of Bleeding Episode[a] [IU/kg]	Bleed	592	37.44 (28.105)	6.8	21.22	30.87	45.22	400.0
Per Bleeding Episode for Maintenance of Hemostasis[b] [IU/kg]	Bleed	34	39.29 (34.206)	10.9	22.26	29.19	43.99	180.7

[a]Only infusions required until resolution of bleed are considered.
[b]Infusions following the resolution of a bleed to maintain hemostasis.

Reduction of Pre-Study Prophylaxis Dosing Frequency

The majority of subjects reduced their pre-study dosing frequency by 30% or more compared to their on-study twice weekly dosing frequency. Of a total of 98 subjects who were on a prophylactic regimen, both pre-study and during the study, the reduction in dosing frequency during the study was:

• 30% or more for 69 (70.4%) subjects

• 20% to < 30% for 1 (1.0%) subject

• 10 to < 20% for 3 (3.1%) subjects

• < 10% for18 (18.4%) subjects

Seven (7; 7.1%) subjects increased or did not change their dosing frequency from pre-study to during the study. Of subjects on prophylaxis during the study, 36 had been on ADVATE, and 82 were on other FVIII replacement therapies during the year prior to study entry (3 subjects had received both ADVATE and another product).

Table 22 Mean and Median Annualized Bleeding Rate by Target Joints at Screening in PPAS - Study 261201

Mean (SD) and Median (Q1 ; Q3) ABRs by Target Joints at Screening in PPAS					
Treatment	**Target Joints[a] (Y/N)**	**Subjects**	**Site: Joint**	**Cause: Spontaneous or Unknown**	**All Sites & Causes**
Prophylaxis	N	32	1.2 (2.4) 0.0 (0.0 ; 1.8)	1.9 (2.9) 0.0 (0.0 ; 2.8)	3.7 (4.4) 3.4 (0.0 ; 5.8)
	Y	69	2.2 (3.2) 0.0 (0.0 ; 2.0)	2.2 (3.7) 0.0 (0.0 ; 2.2)	3.6 (4.9) 1.9 (0.0 ; 6.0)
On-Demand	N	2	22.0 (28.5) 22.0 (1.9 ; 42.2)	35.8 (45.4) 35.8 (3.7 ; 67.9)	40.4 (38.8) 40.4 (13.0 ; 67.9)
	Y	15	36.4 (13.3) 38.1 (24.5 ; 47.7)	24.6 (16.6) 21.6 (11.2 ; 33.2)	40.9 (13.9) 41.5 (31.7 ; 51.1)
[a] Target joints at screening, defined as a single joint with ≥3 spontaneous bleeding episodes in any consecutive 6-month period					

The primary outcome was ABRs. Comparisons between prophylactic and on-demand treatment were based on ABR estimates from a negative binomial regression model, taking into account the treatment regimen, target joints and age at screening, and duration of the OPE (observation period of efficacy).

Ancillary analyses

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application.

These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 23 Summary of Efficacy for trial 261201

Title: A Phase 2/3, Multi-center, Open Label Study of Efficacy, Safety, and Pharmacokinetics of PEGylated Recombinant Factor VIII (Adynovi) Administered for Prophylaxis and Treatment of Bleeding in Previously Treated Patients with Severe Haemophilia A			
Study identifier	261201		
Design	Phase 2/3, multicenter, open-label, 2-arm study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Prophylaxis: ≥50 EDs or 6 months ±2 weeks, whichever occurred last; On demand: approximate duration of 6 months not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Arm A		Prophylaxis: 45 ± 5 IU/kg twice weekly; ≥50 EDs or 6 months ±2 weeks, whichever occurred last; 121 PTPs
	Arm B		On-demand: 10 to 60 IU/kg in event of bleeding; 6 months; 17 PTPs
Endpoints and definitions	Primary endpoint	ABR	Annualized bleeding rate
	Secondary	%Success	Rate of success of Adynovi for treatment of bleeding episodes
	Secondary	#Inf	Number of Adynovi infusions used for the treatment of bleeding episodes
Database lock	March 2016		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	FAS; Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Prophylaxis	On-demand	All
	Number of subject	120	17	<n>
	ABR mean	4.3	43.4	<point estimate>
	95% CI	(3.4; 5.5)	(25.2; 74.8)	<variability>
	%Success	93.1	96.6	96

	95% CI	<variability>	<variability>	0.91; 0.98
	#Inf			
	1	81.3	88.1	85.4
	2	13.5	9.1	10.8

STUDY 261202

This was a Phase 3 prospective, uncontrolled, multicentre study evaluating pharmacokinetics, efficacy, safety, and immunogenicity of Adynovi (pegylated full-length recombinant FVIII) in previously treated paediatric patients with severe haemophilia A

Study Participants

Inclusion Criteria

The main criteria for inclusion were a diagnosis of severe haemophilia A (FVIII <1%) as determined by the central laboratory, or a historical FVIII level <1% as determined at any local laboratory and/or a FVIII gene mutation consistent with severe haemophilia A. Subjects had to be aged <12 years at the time of screening and, based on each subject's medical records, been previously treated with plasma-derived and/or rFVIII concentrate(s) for a minimum of 150 EDs (subjects aged 6 to <12 years) or a minimum of 50 EDs (subjects aged <6 years).

Exclusion Criteria

The main criteria for exclusion were detectable FVIII inhibitory antibodies (≥ 0.6 BU using the Nijmegen modification of the Bethesda assay) as confirmed by central laboratory at screening or a confirmed history of FVIII inhibitory antibodies (≥ 0.6 BU using the Nijmegen modification of the Bethesda assay or ≥ 0.6 BU using the Bethesda assay) at any time prior to screening. Subjects with a known hypersensitivity towards mouse or hamster proteins, PEG or Tween 80, diagnosis of an inherited or acquired haemostatic defect other than haemophilia A (e.g. qualitative platelet defect or von Willebrand's disease) and/or current or recent (<30 days) use of other pegylated drugs prior to study participation or scheduled to use such drugs during study participation were to be excluded.

Treatments

Subjects were to be treated with 50 ±10 IU/kg of Adynovi administered twice weekly. Subjects were to be treated with prophylactic infusions for a minimum of 50 EDs to Adynovi or approximately 6 months, whichever occurred last.

Dosing had to be administered twice weekly, at 3- and 4-day intervals (Option X) or 3.5-day intervals (Option Y with AM and PM dosing) and was to be maintained during the study.

Treatment of Bleeding Episodes

Adynovi was to be used for the treatment of bleeding episodes (ie, breakthrough bleeding episodes during prophylaxis) as soon as possible after occurrence of the bleeding episode, according to the guidelines outlined in the table below.

Table 24 Adynovi treatment guidelines for bleeding Episodes

BAX 855 Treatment Guidelines for Bleeding Episodes		
Severity and Type of Bleeding Episode	**FVIII Level Required (%)**	***Suggested Dose*** **Frequency of Dosing**
Minor Early hemarthrosis, mild muscle bleeding or mild oral bleeding, including epistaxis	20 to 40%	*10 to 20 ±5 IU/kg* Repeat infusions every 12 to 24 hours. Duration: at least 1 day, until the bleeding episode is resolved or healing is achieved
Moderate Moderate bleeding into muscles, bleeding into the oral cavity, definite/more extensive hemarthroses and known trauma	30 to 60%	*15 to 30 ±5 IU/kg* Repeat infusions every 12 to 24 hours for 3 days or more until the pain and acute disability/incapacity are resolved
Major/life-threatening Significant gastrointestinal bleeding, intracranial, intra-abdominal or intrathoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces or iliopsoas sheath, fractures, head trauma	60 to 100%	*30 to 60 ±5 IU/kg* *In case of life-threatening bleeds a dose of 80 ±5 IU/kg may be considered* Repeat infusions every 8 to 12 hours until the bleeding episode/threat is resolved

The required units were to be calculated according to the following formula:

body weight (kg) x desired FVIII rise (%) (IU/dL) x {reciprocal of observed recovery}

A subset of 14 subjects (12 evaluable) within each age cohort was to participate in the PK portion of the study. Prior to the start of the 6-month prophylactic treatment they were to undergo a PK analysis with a single dose of 60 ±5 IU/kg ADVATE followed by a single dose of 60 ±5 IU/kg Adynovi.

Objectives

Primary Objective

The primary objective was a safety outcome, to assess the incidence of FVIII inhibitory antibodies (≥0.6 Bethesda units [BU] using the Nijmegen modification of the Bethesda assay).

Secondary Objectives

The secondary efficacy objectives were:

1. To evaluate the PK parameters of Adynovi in paediatric PTPs <12 years of age

2. To monitor incremental recovery (IR) of BAX 855 over time

3. To evaluate haemostatic efficacy of Adynovi in the management of acute bleeding episodes and for prophylaxis over a period of 6 months

Outcomes / endpoints

Primary Outcome Measure

The primary outcome measure was the incidence of FVIII inhibitory antibodies (≥0.6 BU using the Nijmegen modification of the Bethesda assay).

Haemostatic Efficacy

- Annualized bleeding rate (ABR)
- Consumption of Adynovi: number of infusions and weight-adjusted consumption per month and per year
- Number of infusions per bleeding episode, overall haemostatic efficacy rating at resolution of bleed
- Weight-adjusted consumption per bleeding episode

The subject's response to treatment was assessed using a 4-point efficacy rating scale. Since efficacy rating is based to a large degree on cessation of pain, the Investigator/subject were to, in particular in case of injury-related bleeding into one or more than one location, take the injury-related symptoms into consideration when performing the efficacy rating at resolution of the bleed. The overall clinical efficacy rating was according to the rating scale (refer to table below) at resolution of bleed.

Sample size

A total of 50 subjects <12 years evenly distributed between 2 age cohorts of <6 years and 6 to <12 years was required. To account for potential drop out of subjects, at least 60 subjects were to be enrolled, with 30 subjects in each age cohort. A subset of 14 subjects in each cohort (28 in total) was to undergo a PK assessment with Advate and Adynovi to have 12 evaluable subjects in each age cohort.

Randomisation

This was an open-label clinical study. There was no randomized allocation to study treatment; all subjects were to receive the same dosing schedule of Adynovi.

Blinding (masking)

This was an open-label clinical study, with all subjects receiving the same dosing schedule of Adynovi.

Statistical methods

Statistical Study Conduct

The Statistical Analysis Plan (Version 1.2) was dated 2015 OCT 15. Planned statistical methods were also summarized in the study protocol (Amendment 2 version 2015 MAR 20). The following aspects of statistical interest were modified:

PPAS was added for analyses purposes. The efficacy analyses were to be repeated for the PPAS, which was to contain all subjects in the FAS who fulfilled the compliance criteria.

The set of subjects to be analyzed included all subjects who developed an inhibitor (at any time) and all subjects who did not develop an inhibitor and had ≥50 EDs with an assessment of FVIII inhibitors post 50 EDs.

The ABR was calculated for subjects with less than 6 months of treatment. Since subjects may have bleeds without the adequate duration for treatment, excluding criteria of having at least 6 months of treatment was removed.

Analysis Sets

Full Analysis Set (FAS): The full analysis set (FAS) contained all subjects who received at least 1 dose of Adynovi in either the PK part of the study or prophylaxis part of the study. All efficacy analyses were performed on the FAS. The FAS was the primary analysis set.

Adynovi Safety Analysis Set (BSAS): The Adynovi safety analysis set (BSAS) contained all subjects who received at least 1 dose of Adynovi.

Per Protocol Analysis Set (PPAS): The Per Protocol Analysis Set (PPAS) contained all subjects in the FAS who fulfilled compliance criteria for prophylactic treatment. The PPAS was to be the supportive analysis set.

Statistical Analysis Methods

Inhibitor Rate

The primary outcome measure of the study was the incidence of FVIII inhibitory antibodies, and the objective of the study was to assess the incidence of FVIII inhibitory antibodies during 6 months of twice weekly prophylactic treatment with Adynovi or 50 EDs, whichever occurred last. The number and proportion (Clopper-Pearson exact 95% CI) of subjects who developed inhibitory antibodies to FVIII were to be provided. The set of subjects to be analysed included all subjects who developed an inhibitor (at any time) and all subjects who did not develop an inhibitor and had ≥50 EDs. Only the inhibitory antibodies developed after the first exposure to Adynovi were to be included in the analysis, the inhibitory antibodies developed before the first exposure to Adynovi were to be listed separately.

Number of bleeding episodes during prophylaxis

The primary measure of haemostatic efficacy was the ABR. The annualised rate of bleeding episodes during prophylaxis was to be calculated only for subjects who had adequate treatment time (i.e. 6 months) for ABR assessment. The observation period for the prophylaxis was to be the time between the first and the last prophylactic infusions. The treatment period for surgery was to be excluded from the bleed rate calculation. The annualised rate of bleeding episodes were to be calculated as (Number of bleeding episodes/observed treatment period in days) * 365.2425. The ABR was to be analysed in a generalised linear model framework assuming a negative binomial distribution with a logarithmic link function and presence or absence of target joints and age at screening <6 years versus 6 to <12 years as covariates, and the duration of the observation period in years as an offset. Point and 95% CIs were to be estimated within this model.

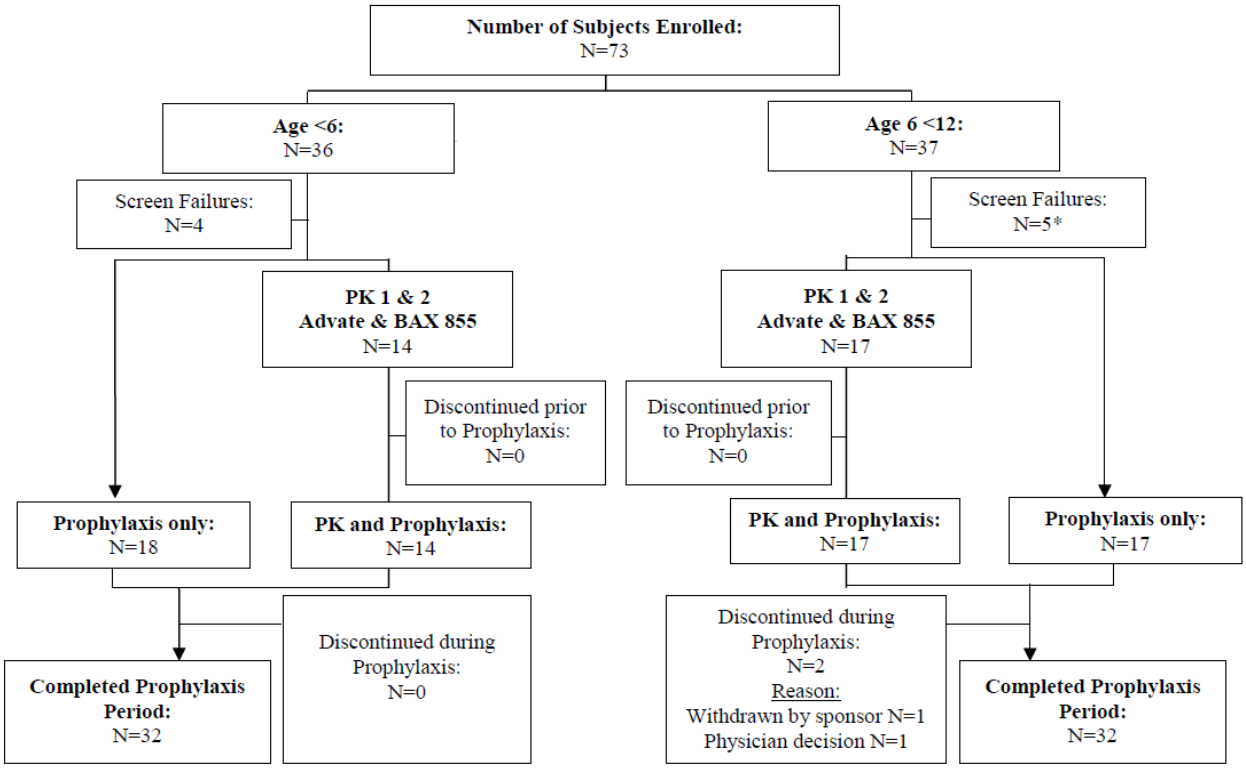
Haemostatic effect in treatment of bleeding episodes

The subject's response to treatment was assessed using a 4-point efficacy rating scale. The proportion of bleeds including 95% CIs for the proportion of bleeds with an efficacy rating of "Excellent" and "Good" (summarized as one entity) were to be presented. The CI was to be determined using an exact Clopper-Pearson test. The 95% CI was to be compared to 70% to implement a hypothesis of a success rate of 70% or less against the alternative hypothesis of more than 70% at the 2.5% level of statistical significance.

Participant flow

Figure 4 Patient disposition STUDY 261202

Figure 1 Subject Disposition Flowchart



* Two subjects counted as Screen Failures were later enrolled (Unique Subject ID 261202-113001 and 261202-511003).

Recruitment

Initiation 2014 OCT 31

Study Completion 2015 OCT 23

Fifty-two (52) study sites in the US, Asia and Europe participated in this study; 39 study sites enrolled subjects and 13 sites were initiated but were inactive.

Conduct of the study

Protocol Amendments

Summary of Significant Changes Adopted with Protocol Amendment 1 (2014 NOV 18)

• The secondary objective “To evaluate changes in HRQoL and health resource use” was changed to become an exploratory objective to harmonize objectives with the description of outcome measures in the protocol where HRQoL and health resource use are described as exploratory outcome measures.

• To avoid potential risk of bleeding episodes in the washout period, the inclusion criterion “The subject has severe haemophilia A (FVIII <1%) as determined by the central laboratory” was amended to “The subject has severe haemophilia A (FVIII <1%) as determined by the central laboratory or a historical FVIII level <1% as determined at any local laboratory and/or a FVIII gene mutation consistent with severe haemophilia A”.

• The threshold for the Nijmegen modification of the Bethesda assay was corrected to ≥ 0.6 BU in the exclusion criteria for consistency with the definition for low responder inhibitory antibodies in other parts of the protocol.

• The planned statistical analysis for the summary PK parameters was amended to follow the approach of Jaki and Wolfsegger (non-compartmental estimation of PK parameters for flexible sampling designs) to allow for summary PK parameters to be estimated irrespective of the feasibility of the population PK model.

• The time point after which no other FVIII concentrate other than Adynovi could be administered was clarified.

• The differential treatment of subjects with bleeding episodes after the start of the Advate PK period and after the start of the Adynovi PK period was clarified.

• The maximum dose of Adynovi for prophylactic treatment was clarified.

• Clarity was added regarding SAE reporting in subjects with port placement/removal.

• The subject’s medical history at screening was clarified to include immunization history.

• An interim analysis could be performed once at least 8 PK evaluations in each of the age cohorts had been completed and an adequate number of EDs had been accumulated in each age cohort.

Protocol Deviations

Protocol deviations were categorised as major or minor in accordance with the criteria set forth in ICH E3 for major deviations. Major deviations were defined as violations from the protocol that were to be evaluated for potential impact to the statistical analysis and/or the interpretation, safety and/or efficacy of the IP. Minor deviations were all deviations that did not have the potential to impact the safety and/or efficacy of the IP. Among a total of 387 protocol deviations in 65/73 (86.7%) subjects enrolled, 380 in 65 subjects were minor and only 7 in 5 subjects were major deviations.

Major protocol deviations included:

• 2 deviations (Category: Other) involving versioning of IC and signature of IC by one parent only in the younger age cohort (Subject 126001)

• 1 deviation (Category: Other) involving timing of IC signature for prophylactic treatment in the older age cohort (Subject 531002)

• 1 deviation (Category Eligibility) in the older age cohort (Subject 253001); this subject had only 89 pre-study exposure days to FVIII and was discontinued from the study by the sponsor

• 2 deviations (Category: IP Administration) involving drug accountability in the younger age cohort (Subject 556001)

• 1 deviation (Category: Protocol Schedule) in the younger age cohort (Subject 527001) involving an IR infusion using vials of different lots

The most frequent minor protocol deviations were procedures not done (189 in 56 subjects, and deviations in the category “investigational product administration (112 in 40 subjects).

Baseline data

Among the 66 subjects who received at least 1 infusion of Adynovi, one (1.5%) was female (Subject 254002), all other subjects (98.5%) were male.

The majority of subjects 43/66 (65.2%) were White, 18/32 (56.3%) in the <6 year and 25/34 (73.5%) in the 6 to <12 year age cohort. Seventeen of 66 (25.8%) subjects, 10/32 (31.3%) in the <6 year and 7/34 (20.6%) in the 6 to <12 year age cohort were Asian. Among the Asians, 1 was Japanese, 4 were Chinese, 2 were Indian, and 10 were reported as "other". Four subjects (4/66; 6.1%) were Black or African American, 2/32 (6.3%) aged <6 years and 2/34 (5.9%) aged 6 to <12 years. In the <6 year age cohort, race was indicated as "other" for one subject and as "multiple" for another. Four of 66 (6.1%) of subjects, 1/32 (3.1%) in the <6 year age cohort and 3/34 (8.8%) in the 6 to <12 year age cohort were of Hispanic or Latino ethnicity.

The mean (SD) age of all subjects was 6.0 (2.70) years. In the <6 years age cohort, the mean (SD) age was 3.7 (1.17) years, in the 6 to <12 years age cohort, the mean (SD) age was 8.1 (1.92) years.

The mean (SD) weight was 17.27 (3.561) kg in the younger and 29.62 (7.599) kg in the older age cohort. The mean (SD) height was 103.80 (9.564) cm in the <6 year and 131.92 (12.676) cm in the 6 to <12 year age cohort.

Table 25 Disease and subjects characteristics - FAS-STUDY 261202

	Statistic	Age <6 Years (N = 32)	Age 6 to <12 Years (N = 34)	Total (N = 66)
Number of Target Joints at Screening				
0	n (%)	29 (90.6)	23 (67.6)	52 (78.8)
1	n (%)	3 (9.4)	3 (8.8)	6 (9.1)
2	n (%)	0 (0.0)	7 (20.6)	7 (10.6)
3	n (%)	0 (0.0)	1 (2.9)	1 (1.5)
Hemophilic Arthropathy				
Presence	n (%)	0 (0.0)	3 (8.8)	3 (4.5)
Absence	n (%)	32 (100.0)	31 (91.2)	63 (95.5)
Historical Average Annualized Bleeding Rate	n	32	34	66
	Mean (SD)	4.3 (3.72)	12.4 (27.29)	8.5 (20.04)
	Median	4.0	3.0	4.0
	IQR (Q1, Q3)	6.00 (0.50, 6.50)	8.00 (1.00, 9.00)	6.00 (1.00, 7.00)
	Minimum, Maximum	0, 12	0, 117	0, 117

Disease and Subject Characteristics
(Study 261202: BAX 855 Full Analysis Set

	Statistic	Age <6 Years (N = 32)	Age 6 to <12 Years (N = 34)	Total (N = 66)
Historical Average Annualized Bleeding Rate Category (Previously Treated on Prophylaxis)				
<1	n (%)	8 (25.0)	5 (17.2)	13 (21.3)
1 to <3	n (%)	4 (12.5)	11 (37.9)	15 (24.6)
3 to <5	n (%)	7 (21.9)	4 (13.8)	11 (18.0)
5 to <7	n (%)	5 (15.6)	5 (17.2)	10 (16.4)
7 to <10	n (%)	3 (9.4)	0 (0.0)	3 (4.9)
10 to <20	n (%)	5 (15.6)	3 (10.3)	8 (13.1)
20 to <30	n (%)	0 (0.0)	1 (3.4)	1 (1.6)
Total	n (%)	32 (100.0)	29 (100.0)	61 (100.0)
Historical Average Annualized Bleeding Rate Category (Previously Treated On-demand)				
7 to <10	n (%)	0 (0.0)	1 (20.0)	1 (20.0)
20 to <30	n (%)	0 (0.0)	1 (20.0)	1 (20.0)
50 to <60	n (%)	0 (0.0)	1 (20.0)	1 (20.0)
>=60	n (%)	0 (0.0)	2 (40.0)	2 (40.0)
Total	n (%)	0	5 (100.0)	5 (100.0)

IQR = Inter quartile range. Q1 = First quartile. Q3 = Third quartile. SD = Standard deviation.
n = Number of subjects in each category. N = Total number of subjects in the relevant analysis set.
% = Percentage of subjects in each category relative to the number of subjects in the relevant analysis set (n/N*100), except for the historical average annualized bleeding rates where percentage are determined from the total number of subjects based on whether subjects were previously treated on prophylaxis or on-demand.
Average annualized bleeding rate based on the 12 months prior to Screening.

The FAS included 66 subjects (65 in the PPAS). Per-protocol analysis set only excluded one subject according to the pre-specified criteria. This subject aged 6 to <12 years (Subject 555003) did not qualify for the PPAS because the subject infused doses below 40 IU/kg for more than 10% of infusions However, 5 more subjects had major protocol deviations and it is not clear whether those have been evaluated for potential impact on the statistical analysis and/or the interpretation, safety and/or efficacy of the IP.

Numbers analysed

Table 26 Distribution of subjects in the data sets -STUDY 261202

	Age < 6	Age 6 to <12	Total
All Subjects Enrolled Set (ENR)	36	37	73
ADVATE Safety Analysis Set (ASAS)	14	17	31
BAX 855 Safety Analysis Set (BSAS)[a]	32	34	66
Full Analysis Set (FAS)	32	34	66
Pharmacokinetic Full Analysis Set (PKFAS)	14	17	31
Per Protocol Analysis Set (PPAS)	32	33	65

[a] All subjects in the ASAS had received BAX 855 and are therefore all included in the BSAS

Outcomes and estimation

Haemostatic Efficacy

A total of 66 subjects received Adynovi for prophylaxis of bleeding at an average mean (±SD) dose per prophylactic infusion of 51.13 (±5.460) IU/kg (median 51.26 IU/kg; range 39.9, 66.8 IU/kg). In subjects <6 years, the average mean (±SD) dose was 51.29 (±4.875) IU/kg (median 51.58 IU/kg; range 42.3, 61.3 IU/kg); in subjects aged 6 to <12 years, the average mean (±SD) dose was 50.99 (±6.029) IU/kg (median 50.42 IU/kg; range 39.9, 66.8 IU/kg).

The average mean (±SD) frequency of infusions per week was 1.82 (±0.170) (median 1.87, range 1.0, 2.0). In the younger age cohort, the average mean (±SD) frequency of infusions per week was 1.86 (±0.057) (median 1.87, range 1.7, 2.0); in the older age cohort, the average mean (±SD) frequency of infusions per week was 1.78 (±0.225) (median 1.85; range 1.0, 1.9).

The mean (±SD) number of prophylactic EDs was 48.45 (±7.679) (median 49.00; range 3.0, 61.0) days. In the younger age cohort, the mean (±SD) number of prophylactic EDs was 50.34 (±3.807) (median 50.00; range 45.0, 61.0); in the older age cohort it was 46.68 (±9.788) (median 49.00; range 3.0, 54.0). A total of 62 subjects, 31 in each age cohort, had at least 50 EDs to Adynovi.

Table 27 ABR and interval between episode- FAS- STUDY 261202

Parameter	Statistic	Statistic Unit	Age < 6 (N = 32)	Age 6 to <12 (N = 34)	Total (N = 66)
Annualized Bleeding Rate	Number of Subjects	n	32	34	66
	Bleeding Rate per Subject	Mean (SD)	2.40 (3.508)	4.76 (9.046)	3.61 (6.988)
		Median	1.95	2.00	2.00
		IQR (Q1, Q3)	3.850 (0.000, 3.850)	5.900 (0.000, 5.900)	3.900 (0.000, 3.900)
		Minimum, Maximum	0, 18.4	0, 49.8	0, 49.8
		Patients Included in Analysis	32	34	66
		Point Estimate for Mean	2.37	3.75	3.04
		95% Confidence Interval for the Mean	[1.486 - 3.778]	[2.429 - 5.781]	[2.208 - 4.186]

IQR = Inter quartile range. Q1 = First quartile. Q3 = Third quartile. SD = Standard deviation.
N = Total number of subjects in the relevant analysis set.
Point estimate and 95% confidence intervals obtained from a generalized linear model assuming a negative binomial distribution with logarithmic link function. The model includes the presence or absence of target joints and age category (< 6 versus >= 6 - <12) as covariates and the duration of the observation period as an offset.

Table 28 ABR by cause- FAS- STUDY 261202

Parameter	Statistic	Statistic Unit	Age < 6 (N = 32)	Age 6 to <12 (N = 34)	Total (N = 66)
		Injury			
Annualized Bleeding Rate	Number of Subjects	n	32	34	66
	Bleeding Rate per Subject	Mean (SD)	1.63 (2.308)	3.71 (8.678)	2.71 (6.471)
		Median	0.80	1.95	1.80
		IQR (Q1, Q3)	2.000 (0, 2.000)	3.900 (0, 3.900)	3.800 (0, 3.800)
		Minimum, Maximum	0, 10.2	0, 49.8	0, 49.8
		Patients Included in Analysis	32	34	66
		Point Estimate for Mean	1.628	2.586	2.089
		95% Confidence Interval for the Mean	[0.989 - 2.679]	[1.639 - 4.080]	[1.492 - 2.925]

Parameter	Statistic	Statistic Unit	Age < 6 (N = 32)	Age 6 to <12 (N = 34)	Total (N = 66)
		Spontaneous/Unknown			
Annualized Bleeding Rate	Number of Subjects	n	32	34	66
	Bleeding Rate per Subject	Mean (SD)	1.05 (2.048)	1.31 (2.467)	1.18 (2.260)
		Median	0	0	0
		IQR (Q1, Q3)	1.900 (0, 1.900)	1.900 (0, 1.900)	1.900 (0, 1.900)
		Minimum, Maximum	0, 10.2	0, 11.5	0, 11.5
		Patients Included in Analysis	32	34	66
		Point Estimate for Mean	1.018	1.316	1.164
		95% Confidence Interval for the Mean	[0.523 - 1.978]	[0.710 - 2.438]	[0.740 - 1.832]

IQR = Inter quartile range. Q1 = First quartile. Q3 = Third quartile. SD = Standard deviation.
N = Total number of subjects in the relevant analysis set.
Point estimate and 95% confidence intervals obtained from a generalized linear model assuming a negative binomial distribution with logarithmic link function. The model includes the presence or absence of target joints and age category (< 6 versus >= 6 - <12) as covariates and the duration of the observation period as an offset.

Over the 6-month prophylactic treatment period, 25/66 (37.9%) subjects had no bleeding episodes, 13/32 (40.6%) in the younger and 12/34 (35.3%) in the older age cohort.

A total of 70 treated bleeding episodes occurred in 34 subjects: 25 treated bleeding episodes in 15 subjects in the younger age cohort and 45 treated bleeding episodes in 19 subjects in the older age cohort. Twenty four out of 65 subjects (37%) experienced no bleeding episodes, 47 out of 65 subjects (72%) experienced no joint bleeding episodes, and 43 out of 65 subjects (66%) experienced no spontaneous bleeding episodes on prophylaxis.

A mean (±SD) of 1.30 (±0.551) infusions (median: 1.00, range: 1.0-3.3) were administered per bleed. The mean (±SD) number of EDs for bleed treatment was 2.74 (±2.538) (median: 2.00, range: 1.0-13.0).

Table 29 Characteristics of bleeding episodes treated with Adynovi

Parameter	Statistic Unit	Statistic	Age < 6 (N = 32/n' = 25)	Age 6 to <12 (N = 34/n' = 45)	Total (N = 66/n' = 70)
Number of Infusions/ Bleed					
1	# of Bleeds	n (%)	22 (88.0)	36 (80.0)	58 (82.9)
2		n (%)	3 (12.0)	3 (6.7)	6 (8.6)
3		n (%)	0 (0.0)	4 (8.9)	4 (5.7)
>=4		n (%)	0 (0.0)	2 (4.4)	2 (2.9)
Efficacy Rating					
Excellent	# of Bleeds	n (%)	15 (60.0)	19 (42.2)	34 (48.6)
Good		n (%)	9 (36.0)	20 (44.4)	29 (41.4)
Fair		n (%)	1 (4.0)	3 (6.7)	4 (5.7)
Not Reported		n (%)	0 (0.0)	3 (6.7)	3 (4.3)
Average Dose/ Infusion to Treat Bleed (IU/kg)	# of Bleeds	n	25	45	70
		Mean (SD)	46.59 (13.649)	41.31 (13.900)	43.20 (13.946)
		Median	48.3	45.5	46.9
		IQR (Q1, Q3)	14.797 (41.013, 55.810)	23.230 (28.087, 51.317)	23.883 (28.394, 52.278)
		Minimum, Maximum	15.5, 66.7	11.2, 75.9	11.2, 75.9
Severity					
Minor	# of Bleeds	n (%)	17 (68.0)	18 (40.0)	35 (50.0)
Moderate		n (%)	8 (32.0)	27 (60.0)	35 (50.0)
Time Since Previous Prophylaxis Dose (h)	# of Bleeds	n	25	45	70
		Mean (SD)	47.77 (22.447)	51.04 (38.370)	49.87 (33.415)
		Median	52.9	47.0	48.2
		IQR (Q1, Q3)	38.600 (31.000, 69.600)	47.500 (24.000, 71.500)	47.500 (24.000, 71.500)
		Minimum, Maximum	0.0, 85.0	0.0, 216.0	0.0, 216.0

IQR = Inter quartile range. Q1 = First quartile. Q3 = Third quartile. SD = Standard deviation.
n' = Number of bleeding episodes treated with BAX 855 in each category.
N = Total number of patients in the relevant analysis set.
% = Percentage of bleeds in each category relative to the number of bleeds in the relevant analysis set.

Table 30 Exposure to Adynovi Infusion- Safety analysis set- study 261202

Table 20
Exposure to BAX855 Infusion
(Study 261202: BAX 855 Safety Analysis Set)

	Statistic Unit	Statistic	Age < 6 (N = 32)	6 <= Age < 12 (N = 34)	Total (N = 66)
		IQR (Q1, Q3)	2.638 (95.801, 98.440)	3.032 (94.766, 97.797)	2.237 (95.801, 98.039)
		Minimum, Maximum	87.1, 101.8	49.8, 100.8	49.8, 101.8
Average dose (IU/kg) per prophylactic infusion	Number of Subjects	n	32	34	66
	Average Dose per Infusion	Mean (SD)	51.29 (4.875)	50.99 (6.029)	51.13 (5.460)
		Median	51.58	50.42	51.26
		IQR (Q1, Q3)	6.223 (48.103, 54.326)	6.149 (47.073, 53.222)	6.159 (47.398, 53.557)
		Minimum, Maximum	42.3, 61.3	39.9, 66.8	39.9, 66.8
Average dose (IU/kg) per month	Number of Subjects	n	32	34	66
	Average Dose per Month	Mean (SD)	458.93 (46.161)	455.86 (76.101)	457.35 (62.919)
		Median	461.93	438.33	456.18
		IQR (Q1, Q3)	65.069 (421.933, 487.002)	65.819 (415.058, 480.877)	67.538 (417.295, 484.832)
		Minimum, Maximum	379.9, 561.5	305.0, 613.8	305.0, 613.8
Average dose (IU/kg) per year	Number of Subjects	n	32	34	66
	Average Dose per Year	Mean (SD)	5507.20 (553.931)	5470.32 (913.210)	5488.20 (755.033)
		Median	5543.19	5259.98	5474.14

The primary outcome was a safety parameter, the incidence of confirmed FVIII inhibitory antibodies (≥ 0.6 BU using the Nijmegen modification of the Bethesda assay).

The proportion of subjects with inhibitory antibody titre ⩾0.6 BU after at least 50 ED to treatment with Adynovi was 0 (95% CI: 0.00-0.06, n = 57). One (3.1%) subject aged <6 years had inhibitory antibodies to FVIII with a titre of ⩾0.6 BU at screening (-56 days prior to first infusion of Adynovi) which was not confirmed upon re-testing. For 7 subjects (2 subjects aged <6 years and 5 subjects aged 6 to <12 years), the inhibitor titre at screening could not be determined. At completion/termination of the study, the FVIII inhibitor titre could also not be determined in 7 subjects (3 subjects aged <6 years and 4 subjects aged 6 to <12 years). Reasons were predominantly an insufficient quantity of samples, but also the presence of fibrin clots in the sample or no specimen received. For one subject who was prematurely withdrawn upon physician's decision, no sample was collected. For the other 6 subjects, results for binding antibodies to FVIII and PEG-FVIII were negative at the completion/termination visit which excludes the presence of an inhibitory antibody to FVIII.

A total of 45 subjects tested negative for binding antibodies at any time point; 16 subjects tested positive for antibodies against FVIII, PEG-FVIII or PEG prior to and 5 subjects tested positive after exposure to Adynovi. There were no persistent non-neutralising antibodies. No subject had antibodies to Chinese hamster ovary (CHO) proteins.

Table 31 Summary of efficacy for trial 261202

Title: A Phase 3 prospective, uncontrolled, multicenter study evaluating pharmacokinetics, efficacy, safety, and immunogenicity of Adynovi (pegylated full-length recombinant FVIII) in previously treated pediatric patients with severe haemophilia A					
Study identifier	261202				
Design	Phase 3, multicenter, uncontrolled				
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Prophylaxis: ⩾50 EDs or 6 months, whichever occurred last; not applicable not applicable			
Hypothesis	Descriptive statistics were presented by age stratum. Point estimates (mean or median) and 95% CIs were computed.				
Treatments	Prophylaxis: 50 ±10 IU/kg twice weekly; as needed for the treatment of bleeding episodes; ≥50 EDs or 6 months, whichever occurred last; 66 PTPs: 32 subjects aged <6 years and 34 subjects aged 6 to <12 years				
Endpoints and definitions	Primary endpoint	INH	Incidence of confirmed factor VIII inhibitory antibodies		
	Secondary	ABR	Annualised bleeding rate; neg. binomial model		
	Secondary	EffRate	Overall hemostatic efficacy rating at resolution of bleed		
	Secondary	#Inf	Number of Adynovi infusions used for the treatment of bleeding episodes		
	Secondary	Consum	Weight-adjusted consumption per year		
Database lock	Date: March 2016				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	FAS; Intent to treat				
Descriptive statistics and estimate variability	Age group	<6	6 -<12	All	
	Number of subjects	32	34	66	
	ABR mean	2.37	3.75	3.04	
	95% CI	(1.486 – 3.778)	(2.429 – 5.781)	(2.208 – 4.186)	
	EffRate Number of bleeds	96% 25	86.6% 45	90% 70	
	95% CI	<variability>	<variability>	80.5% to 95.9%	

	#Inf			
	1	88%	80%	82.9%
	2	12%	6.7%	8.6
	Consum mean (SD)	5507.20 (553.931)	5470.32 (913.210)	5488.20 (755.033)
	Median	5543.19	5259.98	5474.14

Analysis performed across trials (pooled analyses and meta-analysis)

The Applicant has provided an Integrated Summary of Efficacy, which includes data from extension trial 261302. A total of 174 subjects contributed a total of 14946 EDs of Adynovi to the Integrated Summary of Efficacy which has a total of 25578 EDs of Adynovi. No separate analysis for ABRs or haemostatic efficacy ratings has been performed for the extension trial.

Clinical studies in special populations

The inclusion of PTPs aged 65 years or older is no guideline requirement. It is not expected that efficacy differs in this population from that observed in the younger age groups. Also, there are few data on patients with renal impairment, hepatic impairment, and also PUPs.

Supportive study

Surgery trial: Study ID 261204 (Interim Clinical Study Report)

Design

This was a Phase 3, prospective, open-label, single-group, uncontrolled, multicentre study to evaluate the efficacy and safety of Adynovi in approximately 40 male PTPs (≥150 EDs), 2-75 years of age, with severe haemophilia A (FVIII level <1%), undergoing approximately 50 major or minor elective or minor emergency surgical, dental or other invasive procedures.

Objectives

Primary:

- Efficacy: To evaluate the perioperative haemostatic efficacy in above mentioned population undergoing surgery, as determined by the Global Haemostatic Efficacy Assessment (GHEA) score.

Secondary:

- Efficacy: Assessment of intra- and post-operative blood loss; transfusion requirement; occurrence of bleeding episodes; and daily and total weight-adjusted consumption of Adynovi per subject;
- Pharmacokinetics: Assessment prior to major surgeries (IR, AUC0-∞, AUC0-96h,T1/2,MRT, CL, Vss) and IR determination following the initial bolus infusion prior to surgery;
- Safety: occurrence of AEs and changes in vital signs and clinical laboratory parameters.

Treatments and dose

Major surgeries

Prior to surgery, subjects were to receive a loading dose of Adynovi to raise the plasma level of FVIII to 80-100% of normal for major surgeries. After the initial pre-operative loading dose, an optional re-bolus sufficient to raise FVIII levels to the appropriate level as defined for the type of surgery may be administered after a blood sample for FVIII determination has been drawn (preferably within 6-8 hours following surgery) and the required FVIII levels have been determined. The postoperative, pre-infusion FVIII levels should be at least 80% of normal for the first postoperative 72 hours and at least 50% on postoperative Days 4-7. From Day 8 until discharge the FVIII levels should not fall below 30% or as specified in the substitution plan.

Minor surgeries

Prior to surgery, subjects were to receive a loading dose of Adynovi to raise the plasma level of FVIII to 30-60 % of normal for minor procedures. Postoperatively, subjects undergoing minor surgery can be re-dosed postoperatively with Adynovi every 8 to 24 hours. Pre-infusion trough levels of FVIII should be kept at 30-60% of normal for the first 24 hours or longer as deemed necessary by the investigator. At least one postoperative dose should be given; the dose calculation should be based on the individual IR value determined prior to surgery.

For major surgeries, the preoperative loading dose ranged from 36 IU/kg to 109 IU/kg (median: 68 IU/kg); and postoperative total dose ranged from 186 IU/kg to 808 IU/kg (median: 320 IU/kg). The median total dose for major surgeries was 380 IU/kg (range: 249-907 IU/kg) and the median total dose of minor surgeries was 100 IU/kg (range: 76-131 IU/kg).

Study subjects

For the interim analysis of study 261204, a total of 21 subjects were enrolled of whom 19 were unique; 2 subjects re-enrolled. 17 (16 unique) subjects were treated with Adynovi and are included in the safety analysis set (SAS). Fifteen (15) subjects completed the protocol and were included in the full analysis set. Each of these 15 subjects underwent one surgery procedure. All subjects were male and between 19 and 52 years of age. The majority of subjects (16/17 subjects) were white, and one subject was Asian. All subjects except one had a history of haemophilic arthropathy.

Surgeries

The surgical procedures were defined prospectively as major or minor by the investigator/surgeon, based on the guidance in the study protocol.

There were 11 major surgeries: 6 orthopaedic (3 knee replacements, 2 arthroscopic synovectomies, 1 elbow cyst extirpation) and 5 non-orthopaedic procedures (3 dental (multiple tooth extractions including 1 radicular cyst removal), 1 cardiovascular (mediport placement), 1 abdominal (gastric band insertion)).

There were 4 minor surgeries: 1 orthopaedic (synoviorthesis), 1 dental, 1 dermatological and 1 endoscopy (radiosynovectomy) procedure.

Efficacy assessment

Primary objective: Evaluation of the perioperative haemostatic efficacy of Adynovi as determined by the Global Haemostatic Efficacy Assessment (GHEA) score

Assessment by the operating surgeon, 3 individual ratings:

- Intraoperative
- Postoperative (on postoperative Day 1, i.e. the day following the day of surgery)
- Perioperative (at discharge or on postoperative Day 14, whichever is first)

Assessment scale:
Excellent, Score 3: blood loss was less than or equal to that expected for the type of procedure performed in a non-hemophilic population (≤100%)
Good, Score 2: blood loss was up to 50% more than expected for the type of procedure performed in a non-hemophilic population (101-150%)
Fair, Score 1: blood loss was more than 50% of that expected for the type of procedure performed in a non-hemophilic population (>150%)
None, Score 0: Uncontrolled hemorrhage that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy

For assessment at discharge visit or on Day 14, whichever is first, required blood components for transfusion were also taken into account.

Interim results:
Intraoperative: score "excellent" for all 15 procedures.
Postoperative: score "excellent" for 13 procedures. One minor surgery (subject 117001, minor dermatological surgery) was not rated at the time of data cut-off for this report and another minor surgery was rated as "good" (subject 104001, minor dental surgery).
Perioperative: score "excellent" for all 15 procedures.
Subject 104001 was rated as "good" (score = 2) postoperatively, because he had a small amount of oozing of blood from the gums during the night following surgery. After discharge from hospital (6 days after the dental surgery), he had a small bleed which was treated with one dose of aminocaproic acid and one dose of Adynovi. The bleeding stopped immediately and no other recurrent bleeding occurred after that. The subject had an intraoperative blood loss of 5 ml (estimated maximum blood loss predicted preoperatively was 200 mL in a haemostatically normal patient) and an FVII activity level at discharge (postoperative day 1) of 33.7 U/dL (1-stage clotting assay) or 38.1 U/dL (chromogenic assay). These results are within the recommended postoperative range for minor surgeries (30-60% of normal). Therefore, the perioperative haemostatic efficacy of Adynovi at discharge was assessed as "excellent" (score = 3). Overall, the global haemostatic efficacy assessment score was 8 (3+2+3), which corresponds to a rating of "excellent".

Secondary objectives: Determination of 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 Adynovi per subject.

Interim results for blood loss:
Intra- and Postoperative Blood Loss: Intraoperative blood loss was reported for 11 surgeries (9 major and 2 minor surgeries. No intraoperative blood loss (i.e. 0 mL) was reported for one major surgery (arthroscopic synovectomy) and two minor surgeries (synoviorthesis, radiosynovectomy). With a median observed blood loss of 10.0 mL for major surgeries and 2.5 mL for minor surgeries, the actual intraoperative blood loss was considerably lower than the predicted average (median) of 50.0 mL for major surgeries and 2.5 mL for minor surgeries. The median (Q1; Q3) blood loss observed in major surgeries on postoperative Day 1 was 20.0 (0.0 ;

900) mL (maximum: 1200 mL). This was lower than the median maximum blood loss of 50.0 (0.0; 1200) mL predicted preoperatively by the operating surgeons for the types of procedures.

Consumption of Adynovi:
Major surgeries (n=11): The mean ±SD actual daily weight-adjusted dose for major surgeries was 34.35 ±16.756 IU/kg (median: 30.26 IU/kg, range: 9.05-99.19 IU/kg). The corresponding planned value was 35.09 ±17.076 IU/kg (median: 30.69 IU/kg, range: 9.05-100.00 IU/kg).

Minor surgeries (n=4): The mean ±SD daily weight-adjusted dose for minor surgeries was 42.90 IU/kg ±14.839 IU/kg (median: 41.10 IU/kg, range: 20.76-69.31 IU/kg). The corresponding planned value was 44.70 ±16.353 IU/kg (median: 41.10 IU/kg, range: 20.76-69.31 IU/kg).

A sufficient number of surgical procedures (total: 15, major surgeries: 11; additional minor surgeries :4) in 15 patients was performed with Adynovi to ensure proof of its beneficial effect for a bleeding situation and to fulfil the guideline requirements. Type of surgeries included orthopaedic procedures (e.g. knee replacement) and therefore represents a sufficiently challenging model. Study population was chosen appropriately.
The haemostatic effect (primary efficacy endpoint: GHEA score) was assessed as “excellent” for all procedures, except one minor surgery which was rated as “good”. Secondary endpoints support this result. Concerning secondary endpoint “blood loss”, some patients undergoing major surgeries (almost) matched the statistical max. maximum predicted blood loss (e.g. perioperative blood loss in the range of 1210 to 1430 mL, postoperative blood loss of 1200 mL); however without exceeding it. Literature also indicates that blood loss in such surgery can go up to 2000 mL in healthy patients, thus no causal relationship between these high volumes of blood loss and haemophilia A can be drawn.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The design of the two submitted pivotal clinical trials investigating the efficacy (261201 PTPs >12) and 261202 PTPs ≤12) of Adynovi follows and exceeds the requirements of the current guideline for recombinant FVIII products (EMA/CHMP/BPWP/144533/2009 rev. 1) regarding the number and age distribution of subjects included and fulfils the guideline requirements with regards to the number of exposure days observed. In addition, the dedicated surgery trial 261204 provides data supporting the efficacy of Adynovi for the management of haemostasis in major and minor surgical procedures. Extension trial 261302 is currently ongoing and no interim CSR is available. Data from this trial were nevertheless included into the integrated summary of clinical efficay.

A total of 234 subjects received at least one dose of Adynovi. 19 of those subjects were exposed to Adynovi in the phase I safety and PK trial 261101.

In the clinical trials the efficacy of Adynovi was explored for the prevention as well as for the treatment of bleeding events. Trial 261201 investigated the efficacy of Adynovi for prophylactic as well as on-demand treatment in 137 PTPs >12 years of age (Arm A: prophylaxis with 45 ±5 IU/kg once weekly, 120 subjects; Arm B: On demand treatment of BEs, 17 subjects). Trial 261202 investigated the efficacy of Adynovi for the prophylaxis and treatment of bleeds in 66 PTPs ≤12 years age at a prophylactic dose of 50 ±10 IU/kg. The

dedicated surgery trial 261204 contributed data from 11 major and 4 minor surgical procedures in 15 PTPS >12 to the dossier. The extension trial 261302 in 174 subjects is currently ongoing.

The investigated patient population was multi-national and included 66 previously treated children (0-<12 years of age), adolescents (26 adolescents between 13 and 17 years of age) and adults suffering from severe haemophilia A defined as FVIII levels <1%. This fulfils guideline requirements.

The primary endpoint in the paediatric trial 261202 was the incidence of inhibitory antibodies (inhibitors) against FVIII. The endpoints related to efficacy in the pivotal and paediatric trial were defined as follows: Haemostatic effect of Adynovi when used for treatment of bleeds (4 point scale); Number of injections of Adynovi required per bleeding episode; Consumption of Adynovi; Estimated annualised bleeding rate. All of these endpoints are considered appropriate and relevant.

For the evaluation of the effects of BAX 855 in surgery trial 261204, surgeons' assessments of subjects' response to surgery on a 4-point scale as well as intra- and postoperative blood loss, transfusion requirements, bleeding episodes and consumption were defined as efficacy endpoints, fulfilling guideline requirements.

In studies 261201 and 261202, discrepancies were noted between major protocol deviations and criteria for exclusion from the PPAS. The applicant concluded after a thorough review that 31 major protocol deviations in 21 subjects in study 261201, and 7 major protocol deviations in 5 subjects in study 261202, were not impacting safety, efficacy or data integrity. However, there is an inconsistency between the definition of PPAS and the subjects actually selected into that population. Considering that the Full Analysis Set was the primary analysis set and that the PPAS was not crucial for the results interpretation, this was considered acceptable.

Statistical methods in pivotal adult trial 261201

A hierarchical testing of only one primary endpoint (ABR) first and only thereafter testing efficacy as regards hemostatic success in the treatment of bleeds has been predefined. ABRs under prophylactic treatment were estimated using a negative binomial regression model. While the statistical analysis model is appropriate, the specific comparison against the on-demand treatment arm represents a comparison of different patient populations and the interpretation of a 'reduction' of the ABR of at least 50% is not admissible. The applicant provided a comparison of the prophylactic efficacy of Adynovi in patients previously on on-demand treatment versus patients previously on prophylactic treatment and comparing the prophylactic efficacy of Adynovi to the bleeding rate under on on-demand treatment, both in a comparable population of patients previously on on-demand treatment.

For the analysis of the treatment of bleeds; the categorisation of an 'excellent' or 'good' response as treatment success and otherwise as failure, increases the interpretability of the outcome on the otherwise 4-point scale. The bleeds observed within the study are not independent, but stem from repeated bleeds on the same patients. The performed method of a logistic regression model for repeated measurement data is capable to appropriately consider the repeated data structure.

Percentages of subjects in the prophylaxis treatment group were calculated based on 120 subjects, although the FAS included 121 subjects. As only one (0.8%) subject is causing the discrepancy in the analysis set, this issue was overlooked.

Among 118 subjects in the PPAS, 40 subjects reported no bleeding episodes, but Success rate of Adynovi for treatment of bleeding episodes was based on 70 subjects and not 78 as expected. The applicant confirmed that the 8 subjects who were excluded from the analyses actually had reported bleeding episodes. It appears that 7 of them were incorrectly included in the PPAS as they were either not treated or were treated with Advate

instead of Adynovi, which is not in accordance with the definition of the PPAS. Considering that the Full Analysis Set was the primary analysis set and that the PPAS was not crucial for the results interpretation, this was considered acceptable.

Statistical methods in paediatric trial 261202

Inhibitor rate was defined as the primary endpoint and the analysis of the annualised bleeding rate was primary among efficacy analyses. The statistical analysis of the primary endpoint of FVIII inhibitory antibodies was performed using appropriate exact Clopper-Pearson confidence intervals. The use of a two-sided 95% CI is appropriate, but due to the small sample size it is obvious, that this only describes what is scientifically demonstrated rather than allowing for an exclusion of a sufficiently small inhibitor rate.

For the number of bleeding episodes during prophylaxis the annualised bleeding rate was presented based on an appropriate Negative binomial regression model, and providing point estimates as well as 95% confidence intervals. The ABR estimates were calculated using coefficients proportional to the frequencies of classification variables (using 'BYLEVEL OM' as options in the LSMEANS statement) observed in the study, rather than using the default parametrisation of equal coefficients across classification effects. This is considered appropriate, as the study population is considered representative for the population to be addressed. Also sensitivity analyses demonstrated that the two approaches did not provide remarkably different estimates.

The haemostatic effect in the treatment of bleeding episodes was investigated by categorising an 'excellent' or 'good' response as treatment success, and otherwise as failure. This increases the interpretability of the outcome on the otherwise 4-point scale. The statistical analysis was performed using an exact Clopper-Pearson test and 95% confidence intervals, thus ignoring the correlated data structure. Consequently, on request a respective additional analysis considering this correlation was provided, and this demonstrated robustness of the results.

The results of the primary analysis of incidence of FVIII inhibitory antibodies in study 261202 were based on 57 subjects in the Adynovi Safety analysis set. However, a total of 62 subjects have had ≥50 EDs to Adynovi. However, as the binding antibodies to FVIII were negative at the study completion/termination for the 5 subjects who were not included in the primary analysis, presence of a FVIII inhibitor is precluded in these subjects.

Efficacy data and additional analyses

In the pivotal trial 261201 the mean bleeding rates based on estimates from a negative binomial regression model (4.3 and 43.4 in the prophylaxis arm and on-demand arm, respectively) confirm the beneficial effect of prophylaxis with Adynovi observed in this trial. These annualised bleeding rates are in the range of published results from trials with other licensed FVIII products. A substantial number of subjects in the prophylactic arm, 45 (37.5%) reported no bleeding episodes during their treatment period. In contrast, all of the 17 subjects in the on-demand arm reported bleeding episodes during their treatment period. The study was not randomised; subjects were assigned to prophylaxis or on-demand treatment mainly based upon the treatment regimen prior to enrollment. Differences in the baseline data were observed between the treatment arms that can be regarded as two cohorts, thus a comparison between the treatments regimens was considered with care.

Regarding the efficacy in the treatment of bleeding events, in 93.1% of bleeds in the prophylactic arm and 96.6% of bleeding episodes in the on-demand arm, the response to Adynovi was rated as excellent or good. 81.3% in the prophylactic and 88.1% in the on-demand arm were controlled by 1 injection and 13.5% and 9.1% by 2 injections. The median amount of Adynovi needed for the treatment of a bleed was ~ 30 IU/kg.

Haemostatic efficacy ratings declined as bleeding episode severity increased; however, the haemostatic efficacy of treatment was rated excellent or good for a majority of treated bleeding episodes regardless of severity.

The guideline requirement to submit data of a minimum of 5 patients undergoing at least 10 surgical procedures (comprising major surgeries) is exceeded. In the dedicated surgery trial 261204 the efficacy of Adynovi during surgery was investigated through 11 major and 4 minor surgical procedures in 15 subjects. The intraoperative efficacy of Adynovi to provide haemostatic control was rated by the operating surgeon as "excellent" for all 15 procedures.

The postoperative efficacy of Adynovi, as assessed by the operating surgeon on postoperative Day 1 was rated as "excellent" for 13 procedures. One minor surgery was rated as "good" (minor dental surgery) and another minor surgery (minor dermatological surgery) was not rated at the time of data cut-off.

Additional expert consultation

An ad hoc expert group meeting was convened on 28th November 2016 and were asked to respond to the following efficacy question as agreed by CHMP:

How would you consider the potential clinical treatment benefit that Adynovi could provide in the treatment of Haemophilia A?

Overall, Adynovi has modest benefits in terms of prolonged half-life and reduced frequency of administration. The claimed reduction of injections to 2 injections per week may be difficult to achieve in practice as many patients would possibly still require 3 injections per week for prophylactic treatment. Equally, a number of children are able to achieve adequate prophylaxis with just 2 injections of FVIII. Although it was acknowledged that patients using Adynovi 3 times per week would be those requiring a higher trough level and would get greater protection from bleeds.

Lastly, the claimed prolonged half-life is difficult to compare across trials particularly if using different methods of analysis.

Although Adynovi would have represented greater benefits for patients under 12 years (due to lower trough levels for activity, vein access and significant reduction in infusions), due to the existing uncertainties and the modest benefits, the clinical benefit of the treatment cannot be considered positive in children <12 years old. There are concerns about off-label use in children (without any requirement to report adverse events in this population). These concerns would have to be adequately addressed with risk-minimisation measures.

Assessment of paediatric data on clinical efficacy

In the paediatric population of trial 261202 the point estimate for the mean ABR was 2.37 in the <6 years of age cohort, 3.75 in the 6 to ≤ 12 years of age cohort and 3.04 in the total of both age cohorts. The prophylactic dose administered was 50 IU/kg twice weekly in both age cohorts. 25/66 (37.9%) subjects had no bleeding episodes during the treatment period, 13/32 (40.6%) in the younger and 12/34 (35.3%) in the older age cohort. No major bleeds occurred during prophylaxis with Adynovi.

70 treated bleeding episodes were documented during the trial. For 90% of bleeding episodes in the overall population the response to Adynovi was rated as excellent or good, with 96% for younger and 86.6% for older children. Overall, 82.9% were controlled by 1 injection (88% in younger and 80% in older children) and 8.6%

by 2 injections (12% and 6.7%). The median amount of Adynovi needed for the treatment of a bleed was ~ 46 IU/kg in both age cohorts. No new target joints developed during the study.

The median annual consumption of FVIII was 5543.19 for younger children, 5259.98 for older children and 5474.14 IU/kg overall, respectively. These values appear comparable to those observed in other licensing trials with factor VIII products.

2.5.3. Conclusions on the clinical efficacy

The submitted data are considered sufficient to demonstrate the efficacy of Adynovi for the prevention and treatment of bleeding events in patients > 12 years of age with haemophilia A as well as efficacy during surgery. Please see discussion and conclusion on safety (sections 2.6.1 and 2.6.2).

2.6. Clinical safety

The safety data on Adynovi are derived from an Integrated Summary/Analysis of Safety which includes 7 studies, and summaries of the results presented in the individual final clinical study reports from

3 completed studies:

- 261101 (Phase 1)
- 261201 Phase 2/3 (Pivotal)
- 261202 Phase 3 (Paediatric)

4 ongoing studies:

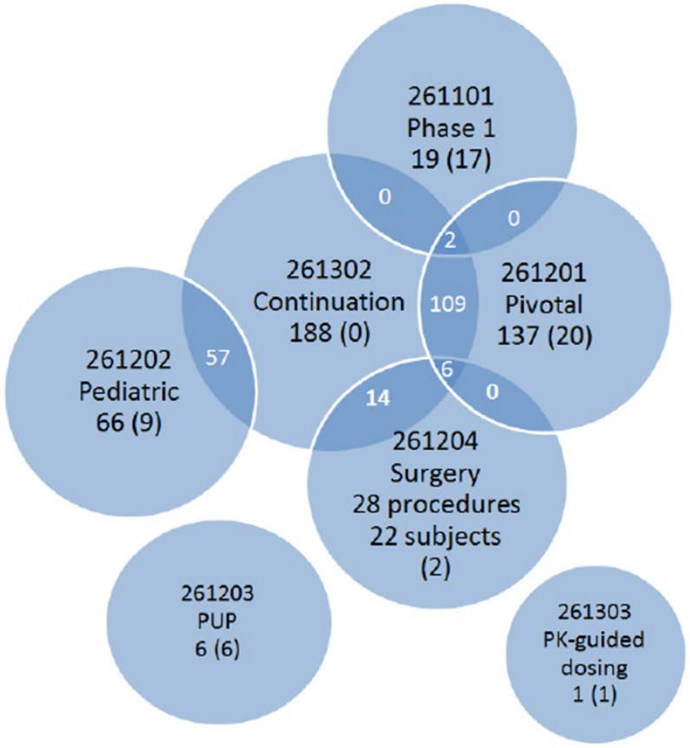
- 261204 Phase 3 (Surgery)
- 261302 Phase 3b (Continuation)
- 261203 Phase 3 (PUP)
- 261303 Phase 3 (PK-guided dosing)

The cut-off date for the data from the 4 ongoing studies was March 2016. The ISS contains detailed clinical data that evaluates the safety profile of Adynovi administered to subjects for prophylaxis, treatment of bleeding episodes, perioperative management, or a single-dose for a PK evaluation. Safety in terms of adverse events (AEs) and immunogenicity were analysed in the age group relevant per EU Guidance: < 6 years, 6 to <12 years, 12 to <18 years, and ≥ 18 years. The demographics, extent of exposure, occurrence of AEs, and antibody development data were pooled for patients who received at least one infusion with Adynovi at any dose, in the above mentioned clinical studies.

Patient exposure

There were 243 unique subjects who received at least 1 infusion of Adynovi who participated in the studies, as depicted in the flowing chart:

Figure 5 Flowchart- subjects disposition in the 7 studies in the integrated safety analysis



Abbreviations: n (x) = the total number of subjects in the study (number of subjects who participated in this single study only).

Note: The total number of unique subjects in the integrated analysis = 243. Six (6) subjects who participated in surgery study more than once are counted separately for each surgery.

A Summary of patient exposure by age group is given in the following tables:

Table 32 Exposure days by Age group – Safey analysis set- Studies 231101, 261201,261202,261203;261204,261302 and 261303

Statistics	<6 years	6 to <12 years	12 to <18 years	≥18 years	All
N	38	34	26	145	243
Mean	75.8	87.5	177.5	139.4	126.3
SD	35.21	27.28	73.21	88.55	80.67
Min	1	9	15	1	1
Q1	70.0	77.0	149.0	55.0	73.0
Median	83.5	88.5	171.5	165.0	111.0
Q3	100.0	108.0	240.0	209.0	196.0
Max	132	130	294	322	322

The overall exposure to Adynovi is provided by age group and by reason for treatment is provided in the following table:

Table 33 Summary of exposure to Adynovi by Age group Safety analysis set- Studies 231101, 261201,261202,261203;261204,261302 and 261303

Age Group = All

Reason for Treatment	Exposure days [days]	Number of Infusions	Total IU Infused [IU]	IU/kg Body Mass Infused [IU/kg]	Average IU/kg per Year[a] [IU/kg/year]
Prophylaxis	28082	28098	90,077,508	1,371,260.12	4,294.51
Treatment of Bleeding Episode	1471	1516	3,766,580	56,301.09	210.54
Maintenance of Hemostasis	105	106	246,619	3,882.46	56.44
PK Study	893	893	2,724,662	50,849.08	NA
Surgery	189	252	673,373	8,814.02	NA
Total	30687	30865	97,488,742	1,491,106.77	NA

Subjects have been exposed for a median (Q1;Q3) of 111.0 (73.0-196.0) exposure days (EDs) during the studies. As can be seen in the tables above, adults and adolescents had a higher exposure to Adynovi than the younger subjects did. It has to be noted, that the paediatric study 261202 was initiated after the pivotal study 261201 was completed. The earlier enrolment and therefore longer participation in the continuation study 261302 might explain the higher exposure in adolescents.

The mean (SD, minimum-maximum) age was 23.4 (15.35, 0-60) years of age and 1/243 subjects was female. Overall, 182 (74.9%) subjects were white, 52 (21.4%) were Asian, 6 (2.5%) were Black or African American, 2 (0.8%) were “other,” and 1 (0.4%) was “multiple.” The majority of subjects in the integrated analysis were adults. Adolescents had the lowest proportion of Asian subjects and the highest proportion of White subjects.

Overall the majority was white, and not Hispanic/Latino. In the paediatric study approximately half of children were < 6 years and half were 6 to <12. There were no children in the surgery trial.

Adverse events

A total of 819 AEs were reported in 182/243 (74.9%) subjects during or after treatment with at least 1 infusion of Adynovi. The overall rate of AEs by infusion was 2.7% (819 AEs/30,865 infusions), the rate of nonserious AEs by infusion was 2.4% (773 AEs/30,865 infusions), and the rate of SAEs by infusion was 0.1% (46 SAEs/30,865 infusions).

Table 34 Overall summary of treated subjects with Adverse Events (Pooled studies)

	N=243 n
Subjects with ≥1 AE	182
Subjects with treatment-related non-serious AEs	10[a]
Subjects with ≥1 SAE	29
Subjects with treatment-related SAEs	0[a]
Deaths	1[b]
Subjects discontinued from the study due to an AE	9

Abbreviations: AE=adverse event; SAE=serious adverse event (during or after infusion with BAX 855).

[a] Relatedness was assessed by the sponsor.

[b] One subject (261201-521001) died of neuroendocrine carcinoma on 22 Feb 2014 after 22 EDs to BAX 855, approximately 3 weeks after withdrawal of BAX 855 on 04 Feb 2014 with the last dose on 01 Feb 2014.

The AEs (regardless of causality or seriousness) that were reported in the highest proportion of subjects were nasopharyngitis 17.7%, upper respiratory tract infections 11.1%, headaches (9.9%), pyrexia (8.2%), diarrhoea (6.6%), cough (6.6%) and arthralgia (7.4%).

Noteworthy, the rate of AEs by infusion was similar for the 2 product configurations: Commercial (294 AEs/10.624 infusions = 2.8%) and non-commercial (346 AEs/14823 infusions = 2.3%). In the case of mixed infusions, the rate was 136 AEs/5253 infusions =2.6%).

During the course of the pivotal study, there was a change in manufacturing facility; from the facility in Thousand Oaks (US) to a facility in Neuchâtel (Switzerland). As a result Adynovi was provided from both facilities in this study. 17.5% of infusions were with the Neuchâtel product, 80.5% of infusions with Thousand Oaks, and 1.2% of infusions with combined, and 0.8% of infusions with unknown product. Since exposure with Neuchâtel product was limited, no statistical analyses or comparisons with Thousand Oaks product could be conducted.

Of the 243 subjects, 176 (72.4%) experienced non-serious AEs, including 14 AEs in 10 subjects, which were considered possibly or probably related to Adynovi treatment by the sponsor. These related AEs included diarrhoea, nausea, headache, and flushing.

The rate of non-serious AEs by infusion was 2.5% (773 AEs/30,865 infusions). The majority of non-serious AEs were mild or moderate in severity.

- Mild: 565 AEs, rate of mild AEs by infusion of 1.8%
- Moderate: 190 AEs, rate of moderate AEs by infusion of 0.6%
- Severe: 17 AEs, rate of severe AEs by infusion of 0.1%
- Missing: 1 AE with a missing severity

Following table displays the AEs that the sponsor assessed as either possibly or probably related to the use of Adynovi:

Table 35 Adverse Drug Reactions and Total AEs for the selected ADR Terms following Adynovi Treatment

MedDRA System Organ Class	Preferred MedDRA Term	Subjects with ADRs (N=243) n (%)	Freq. Category[a]	Total Number ADRs and Rate by Infusion (n=30865)	Freq. Category[a]	Total Number AEs and Rate by Infusion (n=30865)	Freq. Category[a]
Gastrointestinal disorders	Diarrhoea	1 (0.4)	Uncommon	1 (0.003)	Very Rare	18 (0.058)	Rare
	Nausea	2 (0.8)	Uncommon	2 (0.006)	Very Rare	10 (0.032)	Rare
Immune system disorders	Hypersensitivity	1 (0.4)	Uncommon	1 (0.003)	Very Rare	1 (0.003)	Very Rare
Nervous system disorders	Headache	5 (2.1)	Common	8 (0.026)	Rare	42 (0.136)	Uncommon
Skin and subcutaneous tissue disorders	Rash	1 (0.4)	Uncommon	1 (0.003)	Very Rare	4 (0.013)	Rare
Vascular disorders	Flushing	1 (0.4)	Uncommon	1 (0.003)	Very Rare	1 (0.003)	Very Rare
All	All	10		14			

[a] Frequency has been evaluated using the following criteria: Very Common (>=10.00), Common (9.99-1.00), Uncommon (0.99-0.10), Rare (0.09-0.01) and Very Rare (<0.01).

Common adverse events considered related to Adynovi by the applicant were headache (2.1%) and nausea (0.8%). The individual cases of diarrhoea and nausea were assessed as related by both the applicant and the investigator due to their temporal relationship to administration.

From the 14 AEs in 10 subjects, none of these related AEs were serious and no subject has discontinued from any study due to 1 of these events. The only common adverse events assessed as related by the sponsor (in ≥ 1% of subjects) were headache (2.1%) and nausea (0.8%). This is in consistence with the reported safety profile of Advate.

As stated in the interim analysis of study 261204, no adverse events were considered possibly or probably related to Adynovi treatment by the applicant.

Serious adverse event / deaths / other significant events

Deaths

In the pivotal study 261201 one subject (261201-521001) experienced an SAE of neuroendocrine carcinoma that resulted in death after withdrawal from the study (CSR 261201). The subject died on 22 Feb 2014, 21 days after he discontinued treatment with Adynovi (last infusion on 01 Feb 2014) following withdrawal of informed

consent on 04 Feb 2014. The SAE was considered not related to study product by the investigator or the applicant. No safety concerns arise from this event with fatal outcome.

Serious adverse events

A summary of SAEs in the integrated dataset is shown by study below:

Table 36 Overview of Serious Adverse Events of each study

Study Number	Number of SAEs (Number of Subjects)	SAEs of FVIII Inhibitory Antibody	SAEs Related to BAX 855[a]
261101 Phase 1	0 (0)	0	0
261201 Pivotal	5 (5)	0	0
261202 Pediatric	4 (3)	0	0
261204 Surgery	4 (2)	0	0
261302 Continuation	33(20)	0	0
261203 PUP	0 (0)	0	0
261303 PK-guided dosing	0 (0)	0	0
Total[b]	46 (29)	0	0

[a] Assessed by both the investigator and the sponsor.

There were no SAEs reported in phase 1 study 261101, in the PUP study 261203 (to date), or in the PK-guided dosing study 2613013 (to date) and no related SAEs in any of the 5 studies included in the integrated analysis. Throughout the 7 studies included in the integrated analysis, there were a total of 46 SAEs that occurred in 29/243 (10.9%) subjects treated with Adynovi, none of which were considered related to Adynovi as assessed by the investigator and the sponsor.

Other Significant Adverse Events

Allergic reactions / hypersensitivity reactions

There were no AEs considered allergic reactions, as assessed by the applicant, reported in any subject in the integrated analysis.

However, there was 1 AE of urticaria/hives considered an allergic reaction by the investigator. Given the allergic predisposition of the subject with ongoing preexisting allergic symptoms (Subject 261202-126001), the singular occurrence of hives despite continued exposure, the event of urticaria is not considered to be related to Adynovi or a hypersensitivity reaction according to the sponsor's assessment.

Table 37 Non serious Adverse Events that occurred during or after Adynovi Treatment – Safety analysis set- Studies 231101, 261201,261202,261203;261204,261302 and 261303

Subject ID	IP Infusion Start Date/ Time / Stop Date / Time	Preferred Term/ Reported Term	Type	Time after Infusion [h/days]	Onset Date / Time Stop Date / Time	Severity / Relationship a	Action taken	Outcome
261202-126001	2015-05-12T21:15:00 / 2015-05-12T21:20:00	URTICARIA/ HIVES	Systemic	0.25h	2015-05-12T21:30/ 2015-05-13	Moderate/ Possibly Related		Recovered /Resolved

[a]Relationship assessed by investigator.

[a]Study 261101 (Phase I) is excluded from the above listing due to no assessment of thrombotic events were collected during this study.

Further data were provided from study 261203 (PUP study) and study 261303 (PK-guided study) until the cut-off March 2016. Furthermore the cut-off of the previously submitted studies has been extended from October 2015 to March 2016.

In the newly updated data set, 1 AE of a hypersensitivity reaction and 1 AE of a rash were indentified in subject 261203- 524001 from the PUP study. Both AEs were considered related to Adynovi based on the investigator's and the applicant's assessment.

The 2 year old patient with no pathologic findings in his medical history other than severe haemophilia A, had his baseline infusion with Adynovi on 18 January 2016. On 19 January a port was placed at the upper right chest wall. The subject received two infusions of Adynovi on the day of surgery (999 IU and 489 IU respectively, weight 14 kg) and 3 infusions of 489 IU each on 20 January 2016. He then received once daily infusions of 489 IU of Adynovi from 21 to 23 January, followed by infusions of the same dose every other day up to 29 January. On 20 January, i.e. one day following port placement, the subject was reported to have an itchy rash of mild severity which resolved on 1 February 2016. The subject was prescribed 1 mg chlorpheniramine as occasionally required to treat the rash which was considered related to Adynovi. No other concomitant medication was recorded. On 29 January 2016, when withdrawing the needle following the prophylactic infusion, the subject experienced an episode of pallor, flushing and breath holding. Later during this day, the subject developed a non-itchy rash over his shoulders and upper arms considered to be a hypersensitivity reaction related to Adynovi and the subject was subsequently withdrawn from the study. The subject tested negative for binding antibodies to FVIII, PEG and PEG-FVIII at screening, baseline and visit 5 EDs (22 January 2016) whereas at the completion/termination visit he was positive for PEG IgG/IgM (1:160) and PEG-FVIII IgG (1:1280)/IgM (1:320). However, he tested negative for FVIII IgE and PEG-FVIII IgE antibodies at completion/termination.

Injection site reactions

Table 38 Adverse Events of Injection Site Reactions

Preferred Term	Number of Subjects[a] (%) N=243
MEDICAL DEVICE COMPLICATION	1 (0.4)
INJECTION SITE PAIN	1 (0.4)
EXTRAVASATION	1 (0.4)
MEDICAL DEVICE PAIN	1 (0.4)
DEVICE RELATED INFECTION	1 (0.4)
DEVICE RELATED SEPSIS	1 (0.4)
INFUSION SITE HAEMORRHAGE	1 (0.4)
VESSEL PUNCTURE SITE DISCHARGE	1 (0.4)

[a] Adverse Events occuring multiple times for a subject counted once

6 subjects experienced 10 AE that can be considered as reactions related to an infusion. Six of these 10 AEs in 3 subjects are related to an already inserted central venous device. The remaining 4 AEs in 3 subjects are injection site pain (2), vessel puncture site discharge/oozing from venipuncture site (1) and extravasation (1). All 4 AEs were mild, assessed as unrelated and all recovered/resolved.

Thrombotic events

There was 1 non-serious AE of a medical device complication considered a thrombotic event by the investigator in the pivotal study 261201. The event was of mild severity, considered not related to Adynovi by the investigator and the sponsor, and resolved.

Table 39 Non serious Adverse Events that occurred during or after Adynovi Treatment – Thrombotic events Assessed by the Investigator - Safety analysis set- Studies 231101, 261201,261202,261203;261204,261302 and 261303

Subject ID	IP Infusion Start Date/ Time / Stop Date / Time	Preferred Term/ Reported Term	Type	Time after Infusion [h/days]	Onset Date / Time Stop Date / Time	Severity / Relationship [a]	Action taken	Outcome
261201-111001	2013-12-26T19:33:00/ 2013-12-26T19:35:00	MEDICAL DEVICE COMPLICATION/ CATHETER SITE RELATED COMPLICATION	Local	4d	2013-12-30T11:06/ 2013-12-30T11:07	Mild/ Not Related	DOSE NOT CHANGED	Recovered /Resolved
261201-203003[c]	2015-01-20/ 2015-01-20	ARTHRALGIA/ RIGHT ELBOW PAIN	Local	4d	2015-01-24/ 2015-02-05	Mild/ Not Related	DOSE NOT CHANGED	Recovered /Resolved
261202-134003[c]	2015-07-08T15:40:00/ 2015-07-08T15:41:00	HEAD INJURY/ HEAD INJURY-BUMP	Local	6.25h	2015-07-08T21:55/ 2015-07-09T00:00	Mild/ Not Related	DOSE NOT CHANGED	Recovered /Resolved

[a]Relationship assessed by investigator.

[a] Study 261101 (Phase I) is excluded from the above listing due to no assessment of thrombotic events were collected during this study.

[c]The investigators updated the clinical data after the cut-off date, removing the term thrombotic event.

With regards to Listing 3, the applicant has provided a rationale behind the investigators update removing the term thrombotic events from listing 3. According to the applicant the investigators inadvertently listed these two AEs, an arthralgia/right elbow pain in 1 patient and a head injury/head injury-bump in 1 patient as a thrombotic event. Given the nature of these two AEs, a causal relationship to a thromboembolic event can be ruled out.

Laboratory findings

The majority had normal values throughout the study. Abnormal values at baseline are most probably related to pre-existing conditions. It is noted that 18 subjects in the pivotal study had significant increases in ALT/AST. Most of these subjects had infection or reactivation of hepatitis B or C, or the value is abnormal, but not clinically significant.

In the paediatric study one subject had a significant increase in alkaline phosphatase (together with other abnormal values, possibly all accounted for by a viral infection).

Overall, No trends over time were observed for these clinical chemistry and haematology parameters. Abnormal laboratory values were related to the underlying diseases. The data does not imply an impact of Adynovi treatment on Laboratory parameters.

No specific study of hepatic impairment was made. However, patients with history of hepatic associated diseases (e.g. Hepatitis B or C) were included as well in the studies without any evidence for a higher risk for these patients.

Safety in special populations

Age of subjects included in the ISS ranged from 1 to 60 years.

Geriatric Population

Clinical studies of Adynovi did not include subjects aged 65 and over. Safety of Adynovi could therefore not be analysed separately for subjects ≥ 65 years of age.

Use in Pregnancy and Lactation

Clinical experience with Adynovi in pregnant women is not available. Animal reproduction studies have not been conducted with Adynovi. It is unknown whether Adynovi can cause fatal harm when administered to a pregnant woman or can affect reproduction capacity.

There is no information regarding the presence of Adynovi in human milk, the effect on the breastfed infant, or the effects on milk production.

Pediatric Population

Safety and efficacy studies have been performed in 91 previously treated, pediatric patients <18 years of age who received at least one dose of Adynovi as part of routine prophylaxis, on-demand treatment of bleeding episodes, or perioperative management.
Adolescent subjects age 12 to <18 (n=25) were enrolled in the adult and adolescent safety and efficacy trial, and subjects <12 years of age (n=66) were enrolled in a pediatric trial.

Regarding children and adolescents, safety has been investigated in 91 previously treated, pediatric patients <18 years of age who received at least one dose of Adynovi as part of routine prophylaxis, on-demand treatment of bleeding episodes, or perioperative management. Adolescent subjects age 12 to <18 (n=25) were enrolled in the adult and adolescent safety and efficacy trial, and subjects <12 years of age (n=66) were enrolled in a paediatric trial.

Children had a similar rate of SAEs/infusion compared to the other age groups. However, they tended to have a higher rate of non-serious AEs/infusion. The 4 SAEs in children under the age of 12 (Pancytopenia, febrile neutropenia, gastritis, abdominal pain) were not considered related to Adynovi. A greater proportion of adults had SAEs than any other age group. The majority of events considered related by the sponsor were reported in the adult subjects. A somewhat higher percentage of adolescents tended to have more non-serious AEs than subjects in the other age groups.

Overall, no unexpected safety signals emerged in the paediatric subpopulation.

Immunological events

None of the subjects exposed to Adynovi in the integrated analysis developed an inhibitory antibody to FVIII of ≥ 0.6 BU/mL, including:

- 191 subjects with ≥ 50 EDs (95% CI: 0.000 to 0.019)
- 135 subjects with ≥ 100 EDs (95% CI: 0.000 to 0.027)
- 98 subjects with ≥ 150 EDs (95% CI: 0.000 to 0.037)
- 52 subjects with ≥200 EDs (95% CI: 0.000 to 0.068)

The assays for the detection of binding antibodies to FVIII, PEG-FVIII and PEG proteins were established in compliance with recent regulatory guidelines (Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins. CHMP/BMWP/14327/2006) and following the principles described by Whelan et al. A multi-tiered approach including a sensitive ELISA screening assay followed by a confirmatory ELISA assay was used.

For 3 subjects with positive antibody results, based on the previous data provided (data cut- off 2015-10-15) no conclusion could be drawn whether these antibodies were of transient or persistent nature. Additional antibody data became available for 2 subjects, but not for 1 subject (data cut off 2016-03-01):

For 1 subject, no final conclusions can be drawn, because data available until the cut-off date 2016-03-01 suggests an inconclusive pattern with increase of titer at PK baseline and decrease at the 3 months follow up visit (prior to data cut off). Further time points are necessary to confirm whether the AB are of transient or persistent nature.

For another subject, subsequent testing of the AB development in the continuation study 261202 were negative. Therefore it can be concluded, that the AB development is of transient nature in this subject.

For another subjects, no further results are available, because the subject was withdrawn from the study due to non-compliance with the study procedures.

For all 3 subjects, the binding AB did not have an impact on efficacy, PK parameters or observed AE.

According to the newly updated safety data set provided (cut – Off March 2016), the majority of subjects (238/ 243) in the integrated analysis did not develop a persistent binding antibody response against FVIII, PEG-FVIII, PEG, or CHO protein during the studies. 5 of the 243 subjects (3 in the continuation study 261202 and 2 in the PUP study 261203) developed binding antibodies to PEG, PEG-FVIII or FVIII at study completion, at several visits including study completion, or at data cutoff. Based on the current data no conclusion can be drawn whether these antibodies are of transient or persistent nature:

- 1 Subject developed antibodies against PEG-FVIII
- 1 Subject developed antibodies against FVIII
- 1 Subject was positive for IgG antibodies against PEG-FVIII as of the completion/termination visit of study 261202/Screening study 261302 up to the 3-month follow-up visit (data cutoff).
- 1 Subject developed antibodies to PEG-FVIII and PEG which were still present at the time of the data cutoff.
- 1 Subject developed antibodies against PEG and PEG-FVIII at the time of study completion. This subject experienced a mild systemic hypersensitivity reaction which was in temporal association with the IgG/IgM PEG-FVIII and PEG antibodies whereas he tested negative for IgE antibodies against FVIII and PEG-FVIII.

At current state, no final conclusion on the persistence if the AB can be drawn for the five subjects mentioned above. For one subject in the PUP study (261203-524001) a temporal association with an AE related to Adynovi cannot be excluded.

PEG accumulation:

Cases of cellular vacuolation of the choroid plexus epithelial (ependymal cells) have been observed in repeat-dose toxicity studies conducted with proteins PEGylated with molecules ≥ 40 kDA (EMA/CHMP/SWP/647258/2012). The implication of this finding on humans is not conclusive. Although such findings have not been shown in the nonclinical studies conducted so far with Adynovi (20 kD PEG protein part), the duration of these studies (up to 4 weeks) may be too short to reveal cellular vacuolation (at least 6 weeks according to EMA/CHMP/SWP/647258/2012).

The applicant provided further information with regards to AE that were reported beyond the cut-off March 2016 until the thirty-first of July 2017 from the ongoing studies (Study 261203 – PUP study (subjects <6 years old); Study 261302 - Continuation Study (subjects ≤ 75 years old); Study 261303 - Propel Study (subjects 12 to 65 years old)) with special focus on AE that might potentially influence the benefit risk balance from a clinical safety perspective, such as findings with regards to thromboembolic events, allergic/hypersensitivity reactions, inhibitor antibody development or any unexpected safety signals.
With regards to thromboembolic event, no such events have been reported during the period from March 1, 2016 to July 31st, 2017.
FVIII inhibitor development has been observed in one subject in Study 261203 (PUP study). The subject had a total of 227 EDs to Adynovi during the trial. The subject underwent an invasive procedure in April 2016 with inhibitor titres turned negative and remained negative in October 2016. With regards to a second case of inhibitor development (low titre 1.1 BU) which occurred after the cut-of date July, the 31st 2017 in a subject currently being treated on an on demand basis at one of the US study sites, the case is currently being reported to the regulatory authorities and further observation and information is awaited on this case.

With regards to hypersensitivity reactions, 2 cases were reported, one in Study 261302 (continuation study) and one in Study 261303 (PROPEL study). The subject from the continuation study apparently was found to have an allergic predisposition (allergic to the environment in general) with still ongoing symptoms, whereas the hypersensitivity reaction of the subject from the PROPEL study was reported as a drug allergy which resolved at the time of the data cut-off.

Safety related to drug-drug interactions and other interactions

No drug interaction studies have been performed. Formal drug-drug interaction studies are generally not applicable for coagulation factors and no interactions of human coagulation factor FVIII products with other medicinal products have been reported (Core-SmPC for FVIII products). Furthermore, metabolism pathways and CYP involvement are not known to exist regarding coagulation factors.

Discontinuation due to adverse events

9 subjects discontinued due to an AE. These include 4 subjects from the completed study 261201 (Pivotal study), 1 subject from study 261204 (surgery study), and 3 subjects from the ongoing study 261302 (Continuation study). None of these subjects discontinued due to an adverse event considered related to Adynovi by the applicant. 1 subject from the ongoing PUP 261203 study was discontinued due to an AE (Hypersensitivity) considered related to Adynovi by the investigator and the applicant (see also "*Other Significant Adverse Events*" above).

No subject in study 261101 (Phase 1 study) or subject in study 261202 (Pediatric study) discontinued treatment due to an AE.

Table 40 Reasons for the Discontinuations from the studies in the Safety Analysis

Category	261101	261201	261202	261203	261204[a]	261302	261303
Subjects Treated with BAX 855	19	137	66	6	28	188	1
Subjects Discontinued Due to:	0	11	2	1	3	14	1
Adverse Event	0	4	0	1	1	3	0
Physician's decision	0	0	1	0	1[b]	2	0
Subject's decision	0	1	0	0	1	6	1
Other[c]	0	6	1	0	0	3	0

2.6.1. Discussion on clinical safety

The clinical development program of Adynovi is in accordance with the current Guideline for Medicinal Products for Human Use (CHMP) guideline on the clinical investigation of recombinant and human plasma-derived FVIII products.

A first-in-human prospective, open label, crossover, dose-escalation study (study 261101) was performed to evaluate safety and PK parameters of single doses of Adynovi. The study was conducted in adult previously-treated patients (PTPs) with severe haemophilia A (FVIII <1%). This phase 1 study included a total of 19 evaluable adult PTPs. Based on the results of the phase 1 study, the pivotal, phase 2/3, multicentre, non-randomized open label study (study 261201) in adult and adolescent male PTPs with severe haemophilia A was performed to evaluate efficacy, safety, and PK parameters of Adynovi and to assess health-related quality of life (HRQoL) in subjects using a prophylactic dosing regimen or an on-demand treatment regimen. The study included 138 evaluable subjects.

A study in pediatric PTPs <12 years (study 261202) commenced only after the data of 20 PTPs ≥12 years of age who had been treated for ≥50 exposure days (EDs) and the PK data of at least 12 PTPs ≥12 years of age had become available in pivotal study 261201. The phase 3, prospective, uncontrolled, multicentre study evaluated PK, haemostatic efficacy, safety, immunogenicity and HrQoL of Adynovi and included 66 paediatric subjects who received prophylactic treatment.

Four studies are currently ongoing:

- Study 261204 (surgery): A study in subjects undergoing surgery or other invasive procedures. An interim report from this study including 11 major surgeries (6 orthopaedic procedures (3 knee replacements, 2 arthroscopic synovectomies, 1 elbow cyst extirpation) and 5 non-orthopaedic procedures (3 dental (multiple tooth extractions including 1 radicular cyst removal), 1 cardiovascular (mediport placement), 1 abdominal (gastric band insertion) and 4 minor surgeries (1 orthopaedic procedure (synoviorthesis), 1 dental, 1 dermatological and 1 endoscopy (radiosynovectomy) in 15 subjects is available. The results of this interim report indicate that Adynovi is safe, well-tolerated for perioperative management. No deaths and no related serious adverse events occurred.

- Study 261302 (continuation): A continuation study evaluating safety and efficacy in the prophylaxis of bleeding in subjects who have completed previous Adynovi studies. After closure of enrollment for paediatric

study 261202 and pivotal study 261201, the continuation study is open also to Adynovi naïve paediatric and adolescent/adult patients.

- Study 261203 (PUP): A study to evaluate safety and immunogenicity in previously untreated patients (PUPs) <6 years of age and

- Study 261303 (PK-guided dosing): A study to compare the safety and efficacy of PK guided Adynovi prophylaxis targeting two different FVIII trough levels. This study is open to subjects who previously completed another Adynovi study as well as to newly recruited subjects.

An adequate number of PTP subjects have been included to evaluate the safety profile of Adynovi. Adynovi was well tolerated in 243 PTPs with severe haemophilia A from 3 completed (261101, 261201 and 261202) and 4 ongoing (261204, 261302, 261203 and 261303) studies who were treated with Adynovi for prophylaxis, bleeding episodes, and perioperative management or who received a single-dose for a PK evaluation.

One hundred and eighty-eight subjects were treated long-term with Adynovi, by initiating treatment in the phase 1 study, pivotal study, the paediatric study, and the surgery study, and continuing in the ongoing continuation study (Cut Off March2016).

The baseline data shows that the majority of subjects were white. In the paediatric trial there were fewer subjects with target joints and arthralgia compared to the adult subjects, which is expected.

One previously untreated patient in the PUP study 261203 experienced 2 AEs related to Adynovi (minor rash and a mild systemic hypersensitivity reaction) after submission of the MAA. Although both AEs resolved, the subject was withdrawn from the study.

Section 4.8 of the SmPC has been adopted accordingly in order to include the AE “Hypersensitivity” and “rash” in the ADR table.

None of the subjects developed inhibitory antibodies to FVIII of ≥0.6 BU/mL. No persistent binding antibodies to FVIII, PEG-FVIII or PEG developed. 5 subjects (study 261202/study 261302) had antibodies at the time of data cut-off (March 2016), For one subject in the PUP study (261203-524001) a temporal association with an AE related to Adynovi could not be excluded. The applicant claims that no causal relationship of antibodies with AEs or increased occurrence of spontaneous bleeding episodes could be observed. The applicant agreed to follow-up on this issue when providing the final study results of the ongoing studies (please see RMP section). This is considered acceptable, however if new data becomes available which could impact on the safety assessment, the applicant is reminded of its legal obligation to provide these data to the Agency. “Anti-PEG FVIII antibodies” has been added as an important potential risk as part of the safety specification in the RMP.

A mild thrombotic event was identified but this was not considered to be related to Adynovi by the investigator and the applicant. This was considered acceptable.

There were no trends observed over time for clinical chemistry, haematology and lipid parameters or for vital signs. Laboratory Shift Tables by Category and Variable for study 261202 (paediatric study) did not indicate significant changes with regards to relevant chemistry parameters such as creatinine, blood urea nitrogen or total protein or albumin.

A total of 46 SAEs in 29 subjects were reported. None of which were considered related to Adynovi as assessed by the investigator and the applicant. The safety profile for the paediatric population did not raise any safety concerns compared to adolescents and adults included in the studies.

The common adverse events assessed as related by the applicant (in ≥1% of subjects) were headache (2.1%) and nausea (0.9%). This is comparable with the reported safety profile of Advate and has been reflected in section 4.8 of the SmPC.

Cellular vacuolation associated with PEG accumulation

With regards to the safety of PEG and pegylated Pharmaceuticals, the EMA CHMP Safety Working Party discussed the risk for ependymal cell vacuolation caused by PEG (mainly >40 kDa) at an exposure of ≥ 0.4 µmol/kg/month. For Adynovi, the clinical PEG exposure of 6.4 µg PEG/kg BW (70 IU) per day ranges 125 times below the threshold of 0.4 µmol/kg/month. In the repeat dose toxicity study in *Cynomologous* monkey for Adynovi, two animals showed vacuolation in the kidney in the mid dose group (350IU/kg). The vacuolations did not recover after 2 weeks. In addition, it is highlighted that the applicant did not perform non-clinical studies with an acceptable duration (studies lasted up to 4 weeks at most), in comparison with at least 6 weeks requested according to EMA/CHMP/SWP/647258/2012.

The human relevance of kidney vacuolation observed in the preclinical study is unknown. No adverse reactions associated with PEG accumulation were seen in the submitted clinical trials. Uncertainties regarding the relation between formation of vacuoles and the duration of exposure still remain, especially for the paediatric population.

Duration of treatment with Adynovi would be life-long and it is to be expected that unfavourable effects associated with accumulation of PEG would only be detected after long-term exposure over several years. It might be expected that e.g. renal failure or consequences of diminished function of the choroid plexus only occur after treatment for several years, manifesting with potentially unspecific signs and symptoms that develop insidiously over time. Additionally, it is currently unclear which clinical signs or symptoms could optimally serve as (early) markers for negative effects caused by accumulation of PEG in certain tissues/organs.

Based on evidence presented in this dossier, a possible impact of accumulation of PEG in tissues on clinical safety after long-term treatment cannot be excluded with reasonable certainty. However, available safety data derived in clinical trials with Adynovi, although limited with regards to the number of patients, treatment duration and absence of specific monitoring for PEG-associated adverse events, do not reveal any signals hinting to negative effects of PEG accumulation. Moreover, there are a number of other pegylated medicinal products available on the market. Although most of them are intended for short-term treatment and those which can be administered chronically are only licensed for the adult population (e.g. Cimzia), supporting evidence derives from the safety databases of these products including post marketing data. To date there are no safety concerns with regards to PEG accumulation arising from clinical trials and post marketing data from these pegylated products, including pegylated products intended for the chronic treatment of adults.

Therefore, a licence for the treatment and prophylaxis of bleeding in haemophilia A patients with Adynovi can be granted for the adult population.

In contrast, the paediatric population is considered more vulnerable and sensitive to potential detrimental effects of chronic administration of medicinal products due to the ongoing development of the brain and growth of the body. As the magnitude of clinical consequences of the preclinical findings regarding PEG accumulation in the choroid plexus and certain tissues/organs are unclear and no reassuring experience with long-term treatment with other licensed PEGylated products is available in this population, life-long treatment of Adynovi cannot be recommended for paediatric patients in general. The applicant has proposed a licence in adolescent patients 12 years and above which might be acceptable for the following reasons: Excluding children below 12 years of age will reduce the PEG load arising from prophylactic treatment with Adynovi during the entire

childhood. Moreover, most neurodevelopmental milestones are reached in children 12 years of age. Therefore, the potential risks associated with PEG accumulation/vacuolation can be seen differently in children below or above 12 years of age. In consequence, the benefit risk balance has to be assessed separately for all age groups and an indication above 12 years of age can be granted.

Finally, the CHMP is requesting the company to conduct an imposed study in order to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs according to an agreed protocol. The applicant is recommended to discuss the details of this post-authorisation safety study in a scientific advice procedure. In addition, the MAH shall submit the first periodic safety update report for this product within 6 months following authorisation.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional expert consultations

An ad hoc expert group meeting was convened on 28 November 2016 and the experts were asked to respond to the following questions as agreed by CHMP:

Cellular vacuolation of the choroid plexus epithelial cells has been observed in non-clinical studies with≥ 40kDa PEGylated proteins. Could the experts discuss the relevance of these findings and if possible describe potential risks if such accumulation also would occur in humans with special consideration of:

- **prolonged (possibly life-long) treatment**
- **specific problems in children / adolescents**

With regards to the vacuolation it is not clear based on current knowledge what is the translation to humans and actual clinical impact. On one hand, lack of significant clinical findings, evidence of a steady-state, the relatively small PEG molecule and the animal PK studies are reassuring. On the other, the duration of the repeat dose toxicity study is too short to draw firm conclusions as to the absence of long-term effects and long-term safety in human are lacking (current duration of follow-up with PEG-rFVIII is in the order of a few years). Thus, detrimental effects cannot be excluded, especially in younger patients and in case of prolonged treatment.

In the absence of a clear understanding of the distribution and elimination of rurioctocog alfa, especially when the B domain is cleaved from the active protein, it is not possible to fully determine the distribution in human and potential risks of accumulation of PEG in human. Due to these uncertainties and the modest benefits (see below), the clinical benefit of the treatment cannot be considered positive in children <12 years old.

A thorough evaluation of the elimination routes and metabolism mechanisms of PEG would be useful to address these uncertainties.

There is a need to monitor any adverse effects on renal function including proximal tubular and glomerular damage using sensitive markers (serum creatinine clearance and albuminuria might not be sufficient, especially in children, for early detection of albumin and protein in urine).

Possible studies were discussed, including clinical, non-clinical studies and post marketing surveillance. There were different views on the design and feasibility of clinical studies. According to some, clinical studies could be considered. According to others, non-clinical studies in primates could be considered (studies with other species are unlikely to be informative in view of anti-drug antibodies formation after a few weeks of exposure). In any

case, the experts agreed on the need for marketing surveillance reporting and regular updates on long-term exposure data.

Would you consider that the risk of cellular vacuolation of the choroid plexus epithelial cells as observed with ≥ 40kDa PEGylated proteins as well as potential damage to renal function is less likely if a PEG moiety with a lower molecular weight is used (e.g. 20 kDa as for rurioctocog alfa)?

Although damage to renal function is less likely for a PEG moiety with a lower molecular weight (e.g. 20kDa), uncertainty remains with regards to the distribution of the product and how the product behaves. It is not understood how the 20 kDa PEG can be eliminated more easily as it is bound to the B domain of FVIII molecule when FVIII is activated. When PEG is cleaved with the B-domain, the molecule is broken down and is potentially able to cross the epithelial cells if not yet metabolised and eliminated. No biodistribution data in humans are available and these would be needed in order to fully understand the elimination pathway. Monitoring kidney function especially glomerular and tubular function, plasma and urine is recommended (see answer to question No. 1).

How manageable could be a risk related to PEG accumulation in brain structures? Are there solutions to follow and monitor patients and to detect and/or to prevent or reverse adverse events related to PEG accumulation?

Considering the limited non-clinical data available, the difficulty to monitor PEG accumulation as no biomarkers are available and that no long term safety data in humans for Adynovi are available, no conclusions can be drawn with regards to the possibility of managing accumulation in brain structures and potential clinical consequences. In clinical practice, it may not be possible to conduct frequent MRIs unless clinically indicated. Due to these uncertainties and the modest benefits, the clinical benefit of the treatment cannot be considered positive in children <12 years old.

Assessment of paediatric data on clinical safety

Please refer to the above discussion.

2.6.2. Conclusions on the clinical safety

Based on data submitted within this dossier and clinical experience gained with other pegylated products, a licence for the treatment and prophylaxis of bleeding in haemophilia A patients with Adynovi can be granted for the adult population and paediatric patients 12 years of age and above.

The CHMP considers the following imposed Post-Authorisation Safety Study necessary to address issues related to safety:

In order to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs, the MAH should conduct and submit the results of a post-authorisation safety study according to an agreed protocol. The applicant is recommended to discuss the details of this post-authorisation safety study in a scientific advice procedure. In addition, the MAH shall submit the first periodic safety update report for this product within 6 months following authorisation.

2.7. Risk Management Plan

Safety concerns

Table 41: Summary of safety concerns

Important Identified Risks	Inhibitor formation
	Hypersensitivity reactions
Important Potential Risks	Thromboembolic events
	Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs (including in case of off-label use in children below the age of 12 years)
	Anti-PEG FVIII antibodies
	Overdosing (thrombosis) when switching to Adynovi from another FVIII product or underdosing (lack of efficacy/bleeding) when switching from Adynovi to another FVIII product
Missing Information	Use in patients ≥ 65 years of age
	Use in PUPs
	Use of Adynovi for ITI
	Use during pregnancy and lactation

Pharmacovigilance plan

Table 42: On going and planned additional pharmacovigilance studies/activities

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (planned, started)	Anticipated Date For Submission Of Interim Or Final Reports (planned or actual)
Continuation study 261302/ Category 3	To determine the safety of Adynovi based on the incidence of FVIII inhibitory antibody development and to determine the efficacy of Adynovi based on the annualized bleed rate (ABR) of spontaneous bleeding episodes.	-Inhibitor formation -Hypersensitivity reactions --No clinical data on use in patients ≥ 65 years of age	Ongoing	Final CSR: Q4 2018

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (planned, started)	Anticipated Date For Submission Of Interim Or Final Reports (planned or actual)
Paediatric PUP study 261203/ Category 3	The purpose of the study is to investigate the safety, immunogenicity and haemostatic efficacy of PEGylated recombinant FVIII (BAX 855) in PUPs <6 years of age with severe haemophilia A (baseline FVIII level < 1%) and < 3 EDs to ADVATE, BAX 855 or FFP. The primary objective of the study is to determine the safety including immunogenicity of BAX 855 based on the incidence of inhibitor development to FVIII (≥ 0.6 BU/mL using the Nijmegen modification of the Bethesda assay).	-Inhibitor formation -Hypersensitivity reactions --No clinical data on use in PUPs	Ongoing	Final CSR: Q2 2021
PK guided dosing study 261303/ Category 3	The primary objective is to compare two prophylactic dosing regimens of Adynovi targeting two different FVIII trough levels, by comparing the proportions of subjects achieving a total ABR of 0 in the second 6-month study period.	-Inhibitor formation -Hypersensitivity reactions	Ongoing	Anticipated Final CSR: October 2018
Proposed PASS/ Category 1	Safety of Adynovi during long-term routine use in previously treated patients	- Potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs - Thromboembolic events - FVIII inhibitors - Allergic/hypersensitivity reactions	Planned	Submission of protocol: Q4 2018 Submission of study results: Q1-2029

Risk minimisation measures

Table 43: Summary of the risk minimisation measures

Safety Concern	Routine Risk Minimization Activities	Additional Risk Minimization Activities
Inhibitor formation including drug lack of effect	Discussed in the *Warnings and Precautions* section 4.4 of the SmPC. Discussed in the *Undesirable Effects* section 4.8 of the SmPC.	None proposed
Hypersensitivity reactions	Discussed in the *Contraindications* section 4.3 of the SmPC. Discussed in the *Warnings and Precautions* section 4.3 of the SmPC. Discussed in the *Undesirable Effects* section 4.3 of the SmPC.	None proposed
Thromboembolic events	Not applicable	None proposed
Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs (including in case of off-label use in children below the age of 12 years)	Discussed in the *Preclinical safety data* section 5.3 of the SmPC	None proposed
Anti-PEG FVIII antibodies	Not applicable	None proposed
Overdosing (thrombosis) when switching to Adynovi from another FVIII product or underdosing (lack of efficacy/bleeding) when switching Adynovi to another FVIII product	Not applicable	None proposed
Use in patients > 65 years of age	Discussed in the *Pharmacodynamic properties* section 5.1. of the SmPC.	None proposed
Use in PUPs	Discussed in the *Posology* section 4.2 of the SmPC.	None proposed
Use of Adynovi for ITI	Discussed in the *Warnings and Precautions* Section 4.4 of the SmPC.	None proposed
Use during pregnancy and lactation	Discussed in the *Fertility, pregnancy and lactation* Section 4.6 of the SmPC.	None proposed

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Adynovi (rurioctocog alfa pegol) is included in the additional monitoring list as it contains a new active substance and has an imposed PASS.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Haemophilia A is a rare and serious, X-linked, recessive bleeding disorder that predominantly affects males and is characterized by a deficiency of FVIII. In patients with haemophilia A, the primary platelet-driven hemostasis is not affected, but generation of a stable, fibrin-rich clot is defective because inadequate amounts of thrombin are generated. Affected patients suffer from both spontaneous, non-traumatic bleeding episodes as well as substantially prolonged bleeding episodes upon injury. Rarely, life-threatening bleeding may also occur. Patients exhibit variable clinical phenotypes depending on the extent of residual activity (%) of the deficient FVIII that is used to classify the disease severity (WFH, 2012):

- <1% FVIII activity: severe haemophilia A
- 1% to 5% FVIII activity: moderate haemophilia A
- 5% to 40% FVIII activity: mild haemophilia A

Patients with severe haemophilia A bleed spontaneously into joints and muscles, which often results in permanent, disabling joint damage.

3.1.2. Available therapies and unmet medical need

Standard treatment for haemophilia A patients is the replacement of the missing protein by infusion of exogenous FVIII concentrates (as plasma-derived FVIII [pdFVIII] or recombinant FVIII [rFVIII] concentrates). Treatment regimens are either on-demand therapy (given when a bleed occurs) or prophylaxis (which consists of regular infusion of FVIII given every 2 to 3 days to prevent bleeding). In the short term, prophylaxis can prevent spontaneous bleeding and in the long term, prophylaxis can prevent bleeding into joints that will eventually lead to debilitating arthropathy.

Prior to the introduction of clotting factor concentrates in the 1960s, the prognosis for haemophilia A patients was poor, average life expectancy being 15 to 25 years. Major advances in the safety of clotting factor products, including the availability of rFVIII concentrates, the availability of comprehensive haemophilia A treatment centres, the institution of routine prophylaxis, the introduction of home treatment, as well as the active roles that patients take in self-advocacy, have enabled patients with haemophilia A to lead a “close to normal” life.

3.1.3. Main clinical studies

Three trials have been completed in previously treated adolescent and adult patients. Four studies are on-going.

3.2. Favourable effects

The altered PK parameters of Adynovi were characterised in direct comparison to its parent molecule, Advate. In the pivotal trial, the mean half-life of Adynovi was found to be 14.30 hours and that of Advate 10.40 hours with the one-stage assay in 26 patients. In general, AUC, t1/2 and MRT were higher and clearance and Vss lower for Adynovi, while incremental recovery appeared to be similar for both products. The average ratio between the 1-stage clotting and the chromogenic assays for estimation of FVIII activity levels were relatively similar for Advate (0.89) and Adynovi (0.81).

A total of 243 subjects received at least one dose of Adynovi. The investigated patient population was multi-national and included 66 previously treated children (0-<12 years of age), 6 PUPs (<6 years of age), adolescents (26 adolescents between 13 and 17 years of age) and 145 adults suffering from severe haemophilia A defined as FVIII levels <1%. The pivotal study 261201 was an open-label, non-randomised study, with two treatment arms, one with prophylactic regimen with Adynovi at a dose of 45 ± 5 IU/kg twice weekly (n=120) and one arm with on-demand treatment at a dose of 10 to 60 IU/kg (n=17). The mean bleeding rates based on estimates from a negative binomial regression model (4.3 and 43.4 in the prophylaxis arm and on-demand arm, respectively) confirm the beneficial effect of prophylaxis with Adynovi. The paediatric study 261202, was a single-arm, open-label study, with 66 severe haemophilia A subjects divided into two age cohorts; < 6 years (n=32) and 6 to < 12 years (n=34). Subjects were to receive prophylactic treatment with 50 ± 10 IU/kg BW twice weekly. The point estimate for the mean ABR was 2.37 in the <6 years of age cohort, 3.75 in the 6 to ≤ 12 years of age cohort and 3.04 in the total of both age cohorts.

With regards to haemostatic efficacy in the treatment of bleeding events, in 93.1% of bleeds in the prophylactic arm and 96.6% of bleeding episodes in the on-demand arm, the response to Adynovi was rated as excellent or good. 81.3% in the prophylactic and 88.1% in the on-demand arm were controlled by 1 injection and 13.5% and

9.1% by 2 injections. The median amount of Adynovi needed for the treatment of a bleed was ~ 30 IU/kg. In total, 591 bleeding events were treated with Adynovi in the pivotal trial. In the paediatric trial, 70 treated bleeding episodes occurred. For 90% of bleeding episodes in the overall population the response to Adynovi was rated as excellent or good, with 96% for younger and 86.6% for older children. Overall, 82.9% were controlled by 1 injection (88% in younger and 80% in older children) and 8.6% by 2 injections (12% and 6.7%). The median amount of Adynovi needed for the treatment of a bleed was ~ 46 IU/kg in both age cohorts.

Major surgery is a challenging model to establish the haemostatic efficacy of a new coagulation factor. In the dedicated surgery trial 261204 the efficacy of Adynovi during and after surgery was investigated for 11 major and 4 minor surgical procedures in 15 subjects. All evaluable surgeries were assessed as excellent or good by the surgeon. The actual maximum intraoperative blood loss was lower than the predicted loss for healthy individuals.

3.3. Uncertainties and limitations about favourable effects

From a methodological point of view, for the pivotal trial 261201 the comparison against the on-demand treatment arm represents a non-randomized comparison against a different patient population and the interpretation of a 'reduction' of the ABR of at least 50% from this analysis is inappropriate. However, the applicant provided additional analyses on the ABR in order to allow for further assessment of the prophylactic efficacy of Adynovi. This included a within treatment arm analysis of individual on-study versus pre-study bleeding rates using a repeated negative binomial regression model considering the repeated data structure within subjects. In addition, subset analyses comparing bleeding rates on prophylaxis with Adynovi to patients on on-demand Adynovi treatment, both restricted to patients previously on on-demand treatment, as well as the bleeding rate under Adynovi prophylaxis when comparing patients previously on on-demand treatment to patients already previously on prophylaxis provided support for the conclusion of efficacy of Adynovi.

For the paediatric study 261202 ABRs were calculated using a negative binomial regression model. However, this was considered appropriate. Estimates for ABRs were calculated using weights proportional to the frequencies of classification variables observed in the study, rather than using the default parametrisation of equal coefficients across classification effects. This relates to the question on what is to be estimated, i.e. the estimand, and it is agreed that this proportional weighting represents a reasonable approach in this study as the study population is considered representative of the target population.

No patients >65 years of age were included in the studies. There is, however, no reason to expect a different efficacy profile in elderly haemophilia patients as compared to the population studied.

3.4. Unfavourable effects

A non-pegylated in-house reference standard is used for potency measurement of a modified (pegylated) FVIII preparation. Full dose-response curves (including asymptote values) have been provided and verify that the in-house reference standard (HL3AR), Adynovi and the WHO IS behave similarly in both potency assays. However, an observed shift in the assigned value of the current in-house reference standard HL3AR when compared to the WHO IS8, relates to incorrect potency assignment of the previous in-house Reference Standard 08/104. The applicant has changed the specification limits for potency to correct values in IU. Since this leads to an incorrect potency labelling in IU, the applicant has to perform a reassessment of the shift and the specification limits when more data are available. Also further verification of acceptable performance of the chromogenic potency assay in relation to the Ph. Eur method should be verified post approval. Both of these

points will provide confirmation that potency is satisfactorily aligned with the labelled potency in international units and to verify that the same dosage as used in the clinical trials will be delivered by the commercial product.

Adynovi was well tolerated in 243 PTPs with severe haemophilia A in 3 completed (261101, 261201 and 261202) and 4 ongoing (261204, 261302, 261203 and 261303) studies who were treated with Adynovi for prophylaxis, bleeding episodes, and perioperative management or who received a single-dose for a PK evaluation. The common adverse events are headache, diarrhoea, nausea and rash.

There were no AEs of allergic reactions considered to be associated with Adynovi. There was 1 AE of urticaria/hives in study 261202 in a patient with known allergic predisposition and there was no reoccurrence of hives despite continued exposure. 1 AE of a hypersensitivity reaction and 1 AE of a rash were identified in 1 patient from the PUP study related to Adynovi and the subject was withdrawn from the study. 2 cases of hypersensitivity reactions were reported, one in Study 261302 (continuation study, subject with allergic predisposition with still ongoing symptomatic) and one in Study 261303 (PROPEL study, subject with reported drug allergy which resolved at the time of the data cut-off). It is known for FVIII products that hypersensivity reactions are possible and this is reflected in section 4.4 of the SmPC. In addition, hypersensitivity to the active substance, to the parent molecule octocog alfa or to any of the excipients A has been added as a contraindication in section 4.3 of the SmPC.

1 PUP patient in Study 261203 (PUP study) developed neutralising antibodies (inhibitors). The subject had a total of 227 EDs to Adynovi during the trial. There was a second case of inhibitor development (low titre 1.1 BU) in a patient currently being treated on an on demand basis at one of the US study sites, the case is currently being reported to the regulatory authorities and further observation and information is awaited on this case. The risk of anaphylaxis and the correlation between the occurrence of FVII inhibitors and allergic reactions is known for FVIII products and is reflected in sections 4.4 and 4.8 of the SmPC for Adynovi.

3.5. Uncertainties and limitations about unfavourable effects

In the repeat dose toxicity study in *Cynomologous* monkey, two animals showed vacuolation in the kidney in the mid dose group (350IU/kg). The vacuolations did not recover after 2 weeks.

In addition, nonclinical data were limited to 1 month exposure and no studies in juvenile animals were conducted with Adynovi. The non-clinical toxicity data lack to cover the pediatric population below 12 years. Although no neurological symptoms (e.g. tremor) occurred in the clinical studies, accumulation of PEG with possible long-term consequences poses a conceivable risk. Hence, the observed non-clinical effects of the PEG moiety of the molecule are of unknown clinical relevance. It is to be expected that unfavourable effects associated with accumulation of PEG would only be detected after long-term exposure over years.

The safety database is relatively small although it exceeds the guideline requirements. The limited number of subjects only allows for the detection of common and very common adverse events.

The clinical trial programme was not prospectively designed to investigate possible clinical effects of PEG accumulation/vacuolation on the function of presumed main target organs. Accumulation of PEG after long-term treatment has been added as an identified potential risk in the RMP (see section 3.6). The database for Adynovi will be expanded by data gathered in the ongoing studies (extension studies and PUPs study). In addition, the MAH will have to submit the results of an imposed PASS in order to investigate the possible effects of PEG accumulation in the choroid plexus of the brain and other tissues and organs. Finally, the MAH shall submit the first periodic safety update report for this product within 6 months following authorisation.

5 subjects (3 in study 261202 and 2 in study 261302) had PEG-FVIII, FVIII or PEG antibodies at the time of data cut-off (March 2016). However, no final conclusion on the persistence or transience of binding antibodies can be drawn yet. After the cut-off of the current updated data set (July, the 31st 2017) a new confirmed low titre (1.1 BU) inhibitor was reported during the last week of August 2017 which occurred in a subject who was treated on an on-demand basis at one of the US study sites. This case is currently being reported to the regulatory agencies and further observation and information is awaited. "Anti-PEG FVIII antibodies" has been added as an important potential risk as part of the safety specification in the RMP.

3.6. Effects Table

Table 44: Effects Table for Adynovi (data cut-off: March 2016)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
PK	Half-life	h	Adynovi	Advate		Clinical pharmacology section
Pivotal study 261201	Mean t½ (SD)		14.30 (3.838)	10.40 (2.244)	26 patients, comparison at same dose level	
Prevention of bleeding events	Annualised bleeding rate	/year 95% CI	Adynovi		negative binomial regression model	Efficacy Section
261201 pivotal				-		
prophylaxis	N=120		4.3 (3.4; 5.5)			
on-demand	N=17		43.4 (25.2; 74.8)			
261202 paed				-		

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
0-<6 y	N=32		2.37 (1.486 – 3.778)			
6-<12 y	N=34		3.75 (2.429 – 5.781)			
Treatment of bleeding events	4-point scale; excellent + good: treatment success	%			Subjective assessment	
261201 pivotal	For 591 Bleeds		96	-		
261202 paed	For 70 Bleeds		90	-		
	# of infusions to treat the bleed		Adynovi	-		
261201 pivotal			1 (85.4%) 2 (10.8%)	-		
261202 paed			1 (82.9%) 2 (8.6%)	-		
Efficacy in surgery	4-point scale		Adynovi	-	Subjective assessment	
261204 surgery	11 major, 4 minor surgeries in 15 patients		Intra and periop excellent for all 15;	-		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
			postop excellent for 13, good for 1, missing 1			
Unfavourable Effects						
AEs of special interest						Discussion on safety
	Binding Antibodies				In 5 subjects (study 261202/study 261302) no final conclusion on the persistence or transience of binding antibodies can be drawn → data will be submitted with final CSR	
	PEG Accumulation				Potential risk of detrimental effects on tissues and organs can neither be confirmed nor refuted	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The amount of experience in treatment of bleedings and prophylaxis from the performed studies is deemed to be sufficient to conclude that the haemostatic properties of Adynovi are consistent with what is usually observed for other FVIII preparations. The observed major differences in bleeding rates between patients on prophylaxis and the limited number of patients on on-demand treatment are as expected and are also in line with what has been observed in studies of approved FVIII preparations.

In addition to the demonstration of reduced bleeding rates the applicant has demonstrated a slower elimination rate as compared to the non-pegylated corresponding rFVIII molecule with a resulting extended half-life (by approximately 50% on average) in adolescents and adults. The extended elimination allowed less frequent administration in several subjects of the severe haemophilia population studied. The difference between administrations thrice or twice weekly may not appear impressive but 50 less infusions over a year is most probably appreciated by many patients. For other patients, e.g. physically active patients, it may be more important to achieve higher trough levels without changing the administration frequency.

Regular administration of Adynovi was able to resolve target joints: over the course of both studies (261201, 261302 both in PTPs ≥12), for 51 subjects treated twice weekly with Adynovi for ≥18 months, 36/51 patients reported 89 target joints at baseline. After 18 consecutive months of twice weekly prophylaxis with Adynovi, 75/89 target joints had resolved.

The most common side effects are headache, diarrhoea, nausea and rash. The nature and frequency of adverse events does not give rise to concern and do not reveal unexpected safety signals.

Based on evidence presented in this dossier, a possible impact of accumulation of PEG on function of affected tissues/organs after long-term treatment cannot be excluded with reasonable certainty. However, available safety data derived in clinical trials with Adynovi, although limited with regards to the number of patients, treatment duration and absence of specific monitoring for PEG-associated adverse events, do not reveal any signals hinting to negative effects of PEG accumulation.

3.7.2. Balance of benefits and risks

Pertaining to the preclinical and clinical data, the beneficial effects of Adynovi with regards to its ability to replace functional factor VIII and thus to prevent and treat bleeding events and to allow major surgery in patients with severe haemophilia have been satisfactorily shown at an improved treatment interval compared to conventional FVIII products. Furthermore, trough levels in the range of mild haemophilia or even healthy subjects can be reached throughout the majority of the treatment interval which may be a specific advantage of Adynovi as this is likely to have a beneficial impact on target joints, preserve joint function and leads to less morbidity and orthopaedic long-term consequences.

Based on the data from clinical trials with Adynovi and safety data of licensed pegylated products for chronic use in the adult population, approval for the treatment and prophylaxis of bleeding in haemophilia A patients with Adynovi can be granted for the adult population.

The provided safety data did not give rise to concern with regards to the short-term treatment of patients. However, unfavourable effects associated with accumulation of PEG in the choroid plexus of the brain or other tissues or impairment of neural development might only become symptomatic after long-term exposure over several years. No supportive safety data from other pegylated products intended for chronic use are available for the paediatric population. With regards to children below 12 years, at present there is not enough data to conclude and the company should provide additional efficacy and safety data with special considerations on dosing intervals and dosing regimen showing efficacy with even lesser injections. Therefore, the indication in the entire paediatric population cannot be granted. However, the benefit-risk balance has to be seen differently in adolescents compared to children below 12 years of age. Most neurodevelopmental milestones are reached in children below 12 years of age. Moreover, according to literature the treatment compliance generally declines when patients pass from childhood to adolescence. Prophylactic treatment with Adynovi in adolescents with thrice or twice injection per week may lead to improved treatment compliance, could reduce bleeding rates and improve joint health in this patient population and could allow an improved quality of life, thereby outweighing the risks/uncertainties in relation to PEG accumulation and vacuolation.

Considering the above, the CHMP has imposed to the MAH to conduct and submit the results of a PASS in order to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues and organs according to an agreed protocol. The MAH is recommended to discuss the details of the PASS in a scientific advice procedure. In addition, the MAH shall submit the first periodic safety update report for this product within 6 months following authorisation.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Adynovi is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Adynovi is favourable in the following indication:

Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency)

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation safety study (PASS): In order to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs, the MAH should conduct and submit the results of a post-authorisation safety study according to an agreed protocol.	Q1-2029

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that rurioctocog alfa pegol is considered to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0001/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.