26 July 2018
EMA/548301/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dexxience

International non-proprietary name: betrixaban

Procedure No. EMEA/H/C/004309/0000

Note

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

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List of abbreviations

AE	Adverse Event
AF	Atrial Fibrillation
AE	Adverse Event
AIM	Acutely Ill Medical
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
ARR	Absolute Risk Reduction
ASA	Acetylsalicylic Acid
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BID	Twice a day
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CEC	Clinical Events Committee
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human use
CI	Confidence Interval
Cmax	Peak Serum Concentration
CPP	Critical Process Parameters
CrCl	Creatinine Clearance
CRNM	Clinically Relevant Non-Major
CSR	Clinical study Report
CUS	Compression Ultrasound Sonography
CYP	Cytochrome P450
DD	D-dimer
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
DoE	Design of experiments
DMAM	Dymethylamine
DVT	Deep Vein Thrombosis
EC	Executive Committee
ECG	Electrocardiogram
ESRD	End Stage Renal Disease
FSEOP	First Secondary Efficacy Outcome Population
FXa	Factor Xa
GCP	Good Clinical Practice

Hgb	Haemoglobin
HPLC	High performance liquid chromatography
IC	Intracranial
ICH	Intracranial Haemorrhage or International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
INR	International Normalized Ratio
IR	Infrared
ISTH	International Society of Thrombosis and Haemostasis
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
KF	Karl Fischer titration
LDPE	Low Density Polyethylene
LMWH	Low Molecular Weight Heparin
MI	Myocardial Infarction
mITT	Modified Intent-to-Treat
MW	Molecular Weight
NMR	Nuclear Magnetic Resonance
NOAC	Non-vitamin K Antagonist Oral Anticoagulant
NOR	Normal operating range
PAR	Proven acceptable range
Ph. Eur.	European Pharmacopoeia
PD	Pharmacodynamic
PE	Pulmonary Embolism
PEOP	Primary Efficacy Outcome Population
P-gp	Permeability glycoprotein
PK	Pharmacokinetic
PO	Orally / by mouth
PP	Per protocol
PPI	Proton Pump Inhibitor
PSD	Particle size distribution
QD	Once a Day
RR	Relative Risk
RRR	Relative Risk Reduction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SSEOP	Second Secondary Efficacy Outcome Population
TEAE	Treatment Emergent Adverse Event
TG	Thrombin Generation

TGI	Thrombin Generation Inhibition
Tmax	Time of Maximal Concentration
ULN	Upper Limit of Normal
VTE	Venous Thromboembolism

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Portola Pharma UK Limited submitted on 6 December 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Dexxience, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 September 2015.

The applicant applied for the following indication:

Extended prophylaxis of venous thromboembolism (VTE) in adults with acute medical illness and risk factors for VTE.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicant's own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0352/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0352/2016 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 betrixaban 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 20 March 2014. The Scientific Advice pertained to 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: Kristina Dunder Co-Rapporteur: Joseph Emmerich

The application was received by the EMA on	6 December 2016
The procedure started on	23 December 2016
The Rapporteur's first Assessment Report was circulated to all CHMP members on	13 March 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	13 March 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	22 March 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	21 April 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	8 August 2017
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	18 September 2017
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 September 2017
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	12 October 2017
The applicant submitted the responses to the CHMP List of Outstanding Issues on	14 November 2017
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	29 November and 8 December 2017
SAG experts (as appropriate) were convened to address questions raised by the CHMP on The CHMP considered the views of the SAG (as appropriate) as presented in the minutes of this meeting.	6 December 2017
The CHMP agreed on a 2nd list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	14 December 2017

The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on	23 January 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	6 February and 15 February 2018
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	20 February 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Dexxience on	22 March 2018

1.3. Steps taken for the re-examination procedure

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

Rapporteur: Martina Weise Co-Rapporteur: Johann Lodewijk Hillege

The Applicant submitted written notice to the EMA, to request a re-examination of Dexxience CHMP opinion of 26 July 2018., on	09 April 2018
The CHMP appointed Martina Weise as Rapporteur and Johann Lodewijk Hillege as Co-Rapporteur on	26 April 2018
The Applicant submitted the detailed grounds for the re-examination on	28 May 2018
The re-examination procedure started on	29 May 2018
The Rapporteur's re-examination assessment report was circulated to all CHMP members on	27 June 2018
The Co-Rapporteur's assessment report was circulated to all CHMP members on	28 June 2018
The Rapporteurs circulated the Joint Assessment Report on the detailed grounds for re-examination to all CHMP members on	12 July 2018
A meeting of the SAG was convened to consider the grounds for re-examination. The CHMP considered the views of the SAG as presented in the minutes of this meeting.	13 July 2018
The detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP on	24 July 2018
The CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the marketing authorisation on	26 July 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Dexxience is as a direct factor Xa inhibitor for extended thromboprophylaxis in Acute Medically Ill (AMI) adult patients with risk factors for deep vein thrombosis (DVT).

There are three oral direct factor Xa inhibitors currently approved in the EU; apixaban, rivaroxaban and edoxaban. There is also an indirect factor Xa inhibitor, fondaparinux that is administered through subcutaneous injection. The three oral direct FXa inhibitors have been approved in the EU and US for stroke and/or VTE prevention in non-valvular Atrial Fibrillation (AF) as well as for the treatment of pulmonary embolism (PE) and DVT. Apixaban and rivaroxaban have also been approved for use in the prevention of recurrent DVT, PE, and VTE prevention after total knee or hip replacement.

However, none of these compounds are approved for the prevention of VTE in acute medical illness which this application concerns. Indications for the indirect, parenteral factor Xa inhibitor fondaparinux include VTE prevention in patients undergoing surgery but also prevention of VTE in adult medical patients who are judged to be at high risk for VTE and who are immobilised due to acute illness. A similar indication that includes patients with acute medical illness and reduced mobility is found for Low Molecular Weight Heparin (LMWH).

Currently there is no approved or guideline-recommended anticoagulant indicated for extended VTE prophylaxis beyond the 10 ± 4 days of standard therapy as no agent so far has demonstrated a positive benefit: risk ratio for this indication. Three prior studies in extended thromboprophylaxis in hospitalized AIM patients, EXCLAIM, ADOPT, and MAGELLAN, did not succeed in demonstrating a positive benefit: risk balance or a reduction in clinically important symptomatic events with enoxaparin, apixaban, and rivaroxaban, respectively.

2.1.2. Epidemiology

Venous thromboembolism in hospitalised AIM patients is a leading cause of in-hospital mortality despite the use of standard in-hospital VTE prophylaxis. Large randomised trials and observational studies have shown that the risk of VTE, including VTE-related death following hospital admission, continues in high risk AIM patients following discontinuation of standard of care, in-hospital, short-duration (recommended for 10 ± 4 days) VTE prophylaxis with parenteral anticoagulants such as enoxaparin. Of the estimated 400,000 non-fatal VTE events and 150,000 VTE related deaths in acutely ill medical patients annually in G7 countries, more than 50% occur following discontinuation of standard duration prophylaxis (Best Practice & Research Clinical Haematology, 2012; Thromb Haemost, 2009; Hosp Med, 2012).

2.1.3. Clinical presentation, diagnosis

Diagnosis of thrombosis is normally based on investigations such as venous ultrasonography or other vascular imaging procedures (DVT), thoracic spiral CT, lung scan with chest X-ray or pulmonary angiography (PE) guided by clinical symptoms.

2.1.4. Management

Standard of care for VTE prophylaxis includes the use of either low dose unfractionated heparin, fondaparinux, or one of the low molecular weight heparins (LMWH) that are approved for this indication.

VTE prophylaxis is routinely given in situations where the risk for thrombosis is increased immobilization, in conjunction with surgery etc.

About the product

Betrixaban is a novel, orally active, selective, direct, reversible inhibitor of the coagulation factor Xa (FXa). Factor Xa plays a pivotal role in the coagulation cascade because it sits at the junction of the intrinsic and extrinsic pathways of the coagulation system. Inhibition of FXa is expected to exert anticoagulant and antithrombotic effects by decreasing the conversion of prothrombin to active thrombin, thereby diminishing thrombin-mediated activation of the coagulation process, including fibrin formation and platelet activation.

The initially claimed indication for Dexxience was "extended prophylaxis of venous thromboembolism (VTE) in adults with acute medical illness and risk factors for VTE".

During the evaluation, the applicant amended the proposed indication to "prophylaxis of venous thromboembolism (VTE) in adults hospitalised for an acute medical illness (such as acute heart failure, respiratory insufficiency, severe infections, acute rheumatic diseases, or ischemic stroke) who are at risk for thromboembolic complications due to restricted mobility and other risk factors for VTE".

The recommended dose of Dexxience was 160 mg on Day 1, followed by 80 mg taken once daily with food for 35 to 42 days, preferably at the same time each day.

Type of Application and aspects on development

Scientific Advice was sought from the CHMP in March 2014 for the development of betrixaban in the extended prophylaxis of VTE in patients with acute medical illness and risk factors for VTE.

The Applicant sought advice on a number of changes to the Phase 3 pivotal study including:

- The acceptability of change in primary efficacy analysis to a sequential closed hypothesis procedure that tests initially in enriched Cohorts and then the entire Cohort

  The CHMP questioned whether the amended trial would provide results that supported the indication that was, at that time proposed to be: *"Betrixaban is intended for the prevention of VTE in acute medically ill patients."* The CHMP noted that D-dimer is only used to exclude PE from high risk and that its prognostic value of D-dimers to identify high risk patients for DVT should be further supported. The CHMP also advised that the proposal to use an enriched population for the primary analysis and to add in other subgroups sequentially could be

acceptable provided that it could be clearly shown that the decision was not based upon unblinded data and knowledge of treatment effects in the different subgroups of the ongoing study

- The definition of the primary analysis population

The CHMP pointed out that proposed definition of the primary analysis population "all patients that have taken at least one dose of the study medication and have had an adequate assessment of events" does not conform to the ITT principle and the Applicant was asked to consider again, following previous advice, to redefine the primary analysis population as all randomised patients and to put strategies in place for handling missing data.

During the current clinical development, the Committee for Medicinal Products for Human Use (CHMP) Guideline on clinical investigation of medicinal products for the prophylaxis of venous thromboembolic risk in non-surgical patients (CPMP/EWP/6235/04-rev01), published in 2006, was revised in 2016 and came into effect in June 2017.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing betrixaban maleate equivalent to 80 mg betrixaban as active substance. During the assessment the 40 mg strength was withdrawn by the applicant.

Other ingredients are:

Capsule fill: glucose monohydrate, croscarmellose sodium and magnesium stearate.

Capsule shell: gelatin, iron oxide black (E172), titanium dioxide (E171), indigo carmine aluminium lake (E132) and iron oxide yellow (E172).

White printing ink: shellac (E904), propylene glycol (E1520), sodium hydroxide (E524), povidone (E1201), titanium dioxide (E171) and iron oxide black (E172).

The product is packed in HDPE bottle with PP screw cap.

2.2.2. Active Substance

General information

The chemical name of betrixaban maleate is N-(5-chloropyridin-2-yl)-2-[4-(N,N-dimethylcarbamimidoyl)-benzoylamino]-5-methoxybenzamide maleate corresponding to the molecular formula $C_{27}H_{26}ClN_5O_7$. It has a relative molecular mass of 451.91 g/mol and the following structure:

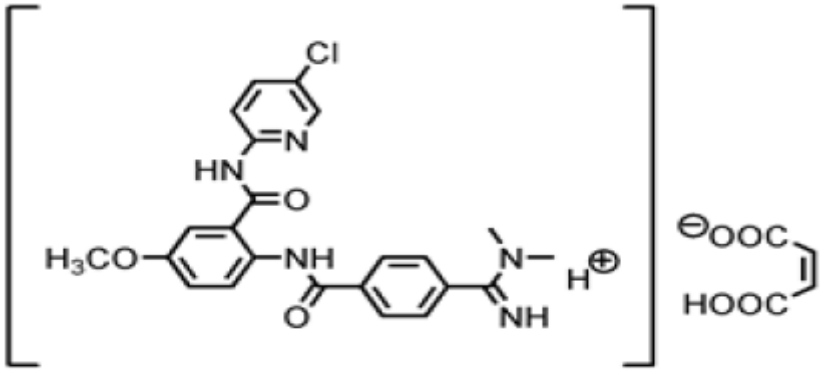


Figure 1 : Active substance structure

The chemical structure of the active substance was elucidated by a combination of infrared spectroscopy (IR), nuclear magnetic resonance (NMR) spectroscopy, high resolution mass spectroscopy, X-ray crystallography, elemental analysis and ultraviolet absorption spectroscopy.

The active substance is a white to yellow solid, with low hygroscopicity, the intrinsic aqueous solubility of betrixaban maleate, determined at 25°C, is 2.7 mg/ml (pH < 5.5).

Betrixaban has a non-chiral molecular structure.

Betrixaban has two polymorphs, designated Form I and Form II. No hydrate or solvate has been observed. Form I is the kinetically stable form with a melting point ranging from 201 to 202°C.

Manufacture, characterisation and process controls

Betrixaban maleate is synthesized in three main steps.

During assessment, the CHMP considered that the synthesis was too short in order to assure robustness during the active substance whole life cycle. Therefore, the applicant was asked to reassign one of the starting materials to an earlier point in the synthesis. The applicant submitted additional information for the starting material providing comprehensive knowledge particularly about impurities and their control, including revised specification and HPLC method for their determination, as well as potential genotoxicity. The CHMP considered the overall response satisfactory. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Critical process parameter (CPP) studies have been performed for all process steps, and the studies have demonstrated that the process is robust with respect to process variations.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The process development program for betrixaban was conducted in compliance with the principles of ICH Q11. Elements of a traditional approach and statistical design of experiments (DoE) were used to identify process parameters and their ranges for the control strategies that have been implemented throughout the manufacturing process. The optimization and the DoE studies have resulted in the proposed commercial manufacturing process. Changes to the three steps process in development were described and the rational for each studied parameter were provided.

For each of the parameters studied, the experimental range, after a reduction taking into account controllability, was used to establish a proven acceptable range (PAR). The narrower, normal operating

ranges (NOR) was defined within the PAR based on the results of optimization studies and process experience.

Design space was not proposed. It was evident from the documentation of DoE study that the manufacturer has gained a deep understanding and knowledge of the process by studying normal operating ranges, proven acceptable ranges and critical process parameters. Since no claims were made regarding design space, these studies were considered as for information.

The specifications and testing for the primary packaging were provided. Bags are certified to fulfil the requirement for articles or component of the articles for pharmaceutical use/food contact as stated in Regulation No. 10/2011 and its amendments.

Specification

The active substance specification includes tests for appearance (visual), identity (HPLC, IR), water content (KF), sulphated ash (Ph. Eur.), X-ray powder diffraction (XRPD), maleate content (IC), assay (RP-HPLC), related substances (RP-HPLC), residual solvents (GC), platinum content (Ph. Eur), elemental impurities (Ph. Eur.), total aerobic counts (Ph. Eur.), total yeast and mould counts (Ph. Eur.), *Escherichia coli* (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of active substance from the proposed manufacturer were stored in a primary packaging , which mimics the commercial packaging for up to 60 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Supporting data from stability studies were also provided.

The following parameters were tested: appearance, water content, X-ray powder diffraction, assay and related substances.

None of the batches showed a significant change from initial results for any attribute tested under long term and accelerated conditions.

Photostability testing following the ICH guideline Q1B was performed on one batch.

Betrixaban from one batch solid was stressed with heat (105°C) and betrixaban sample solutions were prepared and stressed under acidic (0.1 N HCl), basic (0.05 N NaOH), and oxidative (3% H_2O_2) conditions.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 48 months with no special storage conditions in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The 80 mg capsules will be provided as light grey opaque/blue opaque size 2 hard gelatin capsules with "80" printed in black, rectified axially on the body and "PTLA" printed in white, rectified axially on the cap.

The quality target product profile for this product embodies the following attributes for confirmation of oral bioavailability and drug half-life suitable for once-daily dosing:

- Solid oral dosage form suitable for both in-hospital and post-discharge dosing.
- An immediate release dosage form administered not more than twice daily dosing, ideally only once daily dosing.
- Dosage strengths ranging from 10 to 100 mg.
- Suitable for standard package presentations such as bottles and blister cards.
- Shelf life of at least 24 months under room temperature storage conditions

The polymorphic form and the particle size of the active substance have been demonstrated to have no effect on the finished product dissolution profiles. Results of testing by a range of *in vitro* and *in vivo* techniques employed to assess the potential impact of polymorphic form and particle size on the formulation development and pharmacokinetic profile were provided.

During the assessment the 40 mg strength was withdrawn by the applicant.

All the excipients used in the betrixaban capsule formulation are commonly pharmaceutical excipients and meet the standards defined in the current Ph. Eur. monograph, except light grey opaque/blue opaque size 2 hard gelatin capsules. The hard gelatin capsules are commercially available empty capsule shells and are tested according to in-house standards. All the components of the hard gelatin capsules meet the acceptance criteria either in the compendial monograph or in the EU 213/2012. There are no novel excipients used in the finished product formulation. The capsules are coloured and printed using edible, pharmaceutical grade inks in compliance with EC 1333/2008 and EU 231/2012. The list of excipients is included in paragraph 2.2.1 of this report.

Several formulation and process modifications were evaluated throughout the clinical development of the finished product in order to define the proposed commercial formulation and manufacturing process which led to the Phase 3 clinical capsule formulation which then became the intended commercial capsule product. Bioequivalence study was performed showing bioequivalence between the early clinical formulations and the proposed commercial formulation.

The proposed commercial formulation capsule composition was based on the development history of the formulations used in previous clinical studies.

The manufacturing process development program relied on the prior experience of the manufacturer supplemented with studies of certain process parameters using statistical design of experiments (DOE). All of the physical properties of the samples that were generated in the experimental design were within the historical ranges observed during the clinical and primary stability batch manufacture. Even though some processing parameters showed statistical significance, all of the results are acceptable and demonstrate that the process parameters selected for the process constitute the proven acceptable ranges of the process.

The primary packaging is HDPE bottles with HDPE screw caps. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of five main steps.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The proposed in-process tests, critical process steps and process tests were discussed and are considered acceptable. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form for: appearance (visual), identity (UV, HPLC), water content (KF), assay (RP-HPLC), related substances (RP-HPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), total aerobic counts (Ph. Eur.), total yeast and mould counts (Ph. Eur.) and *Escherichia coli* (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for six commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from four commercial scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH), for up 12 months under intermediate conditions (30 ºC / 65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, package appearance, assay, individual and total related substances, dissolution and water content. The analytical procedures used are stability indicating.

No significant changes occur during storage under long term, intermediate and accelerate conditions.

One batch of Betrixaban 80 mg capsules was stressed under acidic (0.1 N HCl), basic (0.1 N NaOH), thermal (105°C), and oxidative (3% H_2O_2) conditions to a target degradation level of 5 to 15% for 15 days.

In addition, one batch of the 80 mg strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

The note for guidance on in-use stability testing of human medicinal products (CPMP/QWP/2934/99) identifies a need for inclusion of an 'in-use shelf-life' for medicinal products packaged in large volumes and intended for a longer in-use shelf-life. Taking into consideration the nature of the product and its stability, as demonstrated by data from product development, accelerated stability and long term stability, the conduct of an in-use stability program would give limited additional stability data to

support pharmacy dispensing. There is no concern for potential degradation of the formulated product during use. There are no factors of concern for in-use stability data to be tested for this product.

Based on available stability data, the proposed shelf-life of 24 months without any special storage conditions are acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable. 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.

2.2.6. Recommendation for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Betrixaban (also referred to in this report as PRT054021, MLN1021, CT054021, MK-4448) is a small molecule that selectively blocks the active site of factor Xa (FXa). By directly inhibiting FXa, betrixaban decreases thrombin generation with no direct effect on platelet aggregation.

Preclinical evaluation of the anti-thrombotic and anti-haemostatic effects of oral betrixaban was performed by the applicant in mice, rats, rabbits, monkeys, and baboons. *In vivo* antithrombotic efficacy of betrixaban was studied in two well-established venous thrombosis models. The efficacy of betrixaban in inhibiting arterial thrombus formation was studied in a ferric-chloride (FeCl3)-induced thrombosis model in rats. Bleeding effects from betrixaban administration were also evaluated in mice (tail transection blood loss), rabbits (cuticle bleeding time) and monkeys (template bleed time).

2.3.2. Pharmacology

Primary pharmacodynamic studies

A summary of the *in vitro* and *in vivo* primary pharmacology studies conducted with betrixaban are summarised in **Tables 5** and **6** respectively.

Table 5. *In vitro* primary pharmacology studies performed with betrixaban

Type of study, study number	Test system/ Test condition	Results
Betrixaban		
In Vitro Potency and Selectivity NC-15-0616	Purified serine protease enzymatic cleavage of a peptidyl substrate in a buffered system	Human fXa: Ki = 117 pM Betrixaban inhibited human prothrombinase in a non-competitive manner with mean Ki = 801 pM Human fXa/betrixaban inhibitor complex dissociates at a slow rate with an off rate (k_{off}) of 0.02 s^{-1}. The k_{on} was 56 μM-1s^{-1}.
In Vitro Characterization of Anti-Thrombotic Mechanism NC-15-0712	Human plasma Human whole blood Rabbit whole blood <u>Betrixban concentration:</u> fXa in PPP: 0-1 μM TG in RT-PPP: 0-25 μM Platelet-mediated TG in RT PPP Whole blood TG: 0-2 μM PPP PT: 0-2 μM. PPP aPTT: 0-1 μM. Whole blood PT: 0-0.5 μM Whole blood aPTT: 0-1 μM Rabbit whole blood PT: 0-1 μM TAT and F1+2 levels: 200 nM Human platelet aggregation: 0-100 μM	FXa activity in human, PPP: IC50 = 6.9 nM. Concentration to obtain 2-fold increase in lag time in fibrinogen free plasma (reptilase treated PPP): 0.36 μM. Concentration to obtain 2-fold increase in lag time in platelet-mediated thrombin generation assay: 8 nM. Concentration to obtain 2-fold increase in lag time in whole blood thrombin generation assay: 90 nM. Doubling of PT in hu PPP: 550 nM Doubling of aPTT in hu PPP: 400 nM. Doubling of PT in human whole blood: 200 nM Doubling of aPTT in human whole blood: > 1 μM Dose-dependent prolongation of PT in rabbit whole blood. Approximately 4-fold higher concentrations of betrixaban were required to inhibit clotting in rabbit blood (IC_{50} ~200 ng/mL in human blood vs. ~800 ng/mL in rabbit blood). Inhibition of TAT and F1+2 levels: both decreased by 200 nM betrixaban
In Vitro Thrombin Generation PD activity of fXa inhibitors in plasma NC-16-0745	Human plasma Thrombin generation in plasma (TF ~100 pM) Betrixaban: 0-250 nM Rivaroxaban: 0-250 nM Apixaban: 0-1,000 nM	In TF-initiated thrombin generation assay in human plasma, betrixaban was more potent than the other two fXa inhibitors, with estimated values: IC50 = 57.9 nM (betrixaban), IC50 = 137.2 nM (rivaroxaban) IC50 = 449.8 nM (apixaban)

PPP = Platelet poor plasma, PT = Prothrombin time TG = thrombin generation

Table 1. ***In vivo*** **primary pharmacology studies performed with betrixaban**

Type of study, study number	Test system/ Test condition	Results
In vivo Tail Transection NC-10-0325	Mouse/ C57Bl/6, M, n=9-10 Oral gavage 2, 10, 20, 40, 50, 100, 400 mg/kg Betrixaban 100 mg/kg/day aspirin Betrixaban (50, 100 mg/kg) was administered to mice, with and without aspirin in the drinking water, 30 min prior to tail transection. In a separate set of studies, betrixaban was administered alone at various dose levels 2 hours prior to tail transection.	In the first study, no statistically significant increase in blood loss was seen for betrixaban, compared with vehicle; however, a significant increase in bleeding time was observed at 100 mg/kg betrixaban ($p = 0.0473$ vs. vehicle). In a second study, a significant increase in blood loss was observed at 100 mg/kg ($p = 0.0312$ vs. vehicle). Co-administration of betrixaban with aspirin significantly increased blood loss ($p < 0.0003$, 100 mg/kg betrixaban + aspirin vs. vehicle). In the third study, betrixaban alone at 400 mg, significantly increased blood loss following tail transection ($p = 0.0145$, vs. vehicle).
In vivo Cardiovascular/ Thrombosis NC-12-0464	Male rats: 10/group for each test agent 24/group for vehicle Oral gavage and IV bolus + infusion 0.01, 0.1, 1 mg/kg, PO clopidogrel; 0.2, 0.7, 2.0 mg/kg, IV betrixaban. Combination: 0.01 mg/kg, PO clopidogel + 0.2 mg/kg, IV betrixaban	Both betrixaban and clopidogrel demonstrated a dose- dependent inhibition of carotid artery occlusion in this rat $FeCl_3$ induced thrombosis model. At the high dose of betrixaban (2 mg/kg; 0.5 µM plasma concentration), 9/10 arteries did not occlude. At the high dose of clopidogrel (1 mg/kg), 9/10 arteries did not occlude. The combination of two low doses of betrixaban and clopidogrel showed patency rate of 70%.
In vivo Deep Vein Thrombosis (DVT) NC-15-0703	Male Rabbit, New Zealand White N=6-9/group IV bolus, followed by infusion 1, 3, 6 mg/kg <u>Method:</u> In this model, fibrin-mediated thrombus formation is induced by the insertion of cotton threads into the vena cava. Efficacy is determined by the amount of thrombus accretion on the cotton threads measured by weight over a period of 2 hours.	Betrixaban showed dose-dependent inhibition of thrombus accretion and prolongation of coagulation parameters in the rabbit DVT model: Mean clot weight was significantly reduced in the groups treated with 3 and 6 mg/kg betrixaban ($p = 0.02$ and $p = 0.005$, respectively, vs. vehicle). No effect on Betrixaban on clot formation was observed at 1 mg/kg. The mean plasma levels required to significantly inhibit venous thrombus accretion were approximately 1.75 µM Ratios of coagulation parameters measured before and after betrixaban administration showed an approximate 2-fold prolongation of PT at a dose of 3 mg/kg and an approximate 3-fold prolongation of PT at a dose of 6 mg/kg. aPTT was prolonged approximately 2-fold at both the 3 and 6 mg/kg dose levels, compared with vehicle alone.

Type of study, study number	Test system/ Test condition	Results
Cuticle Bleeding Time (CBT) NC-15-0711	Male Rabbit, New Zealand White N=6-10 IV bolus 1, 3 mg/kg IV betrixaban; bolus (0.125 and 0.374 mg/kg, respectively) followed by infusion (0.878 and 2.633 mg/kg, respectively, at 0.25 mL/min for 2 hours) <u>Method:</u> Cuticle bleeding time was measured following a standardized incision in the toe nails of anesthetized rabbits.	At a dose of 3 mg/kg (~1.75 µM plasma concentration), betrixaban increased bleeding time by approximately 2 fold at 50 minutes post-administration (p = 0.0162 vs. vehicle). At this dose level, coagulation markers (PT, aPTT) were increased by ~2-fold, compared with vehicle. A non-significant effect in bleeding time was observed at 90 minutes post-administration (p > 0.05 vs. vehicle at 90 minutes). The lower dose of betrixaban (1 mg/kg) did not increase CBT at any time point (Cave = 0.63 µM), relative to the vehicle group.
Template Bleed Time (TBT) NC-10-0323	Male Rhesus Monkey, N=4 Oral via nasogastric tube 4.0, 7.5 mg/kg, PO Betrixaban 325 mg Aspirin	Single oral dose of betrixaban alone did not increase TBT up to a dose of 7.5 mg/kg (Cave = 0.5 µM)
Artery-vein (A V) Shunt Thrombosis NC-06-0041	Male Baboon, N=3-4 IV Infusion (betrixaban, razaxaban); SC fondaparinux <u>Betrixaban</u> 0.5, 0.114, 0.206, 0.480 mg/kg baboon Bolus + infusion <u>Method</u>: In this model, a 2-component thrombogenic device measures thrombus growth on a Dacron graft and in an expansion chamber.	Betrixaban inhibited thrombus formation in the low shear expansion chamber with mean plasma concentrations of approximately 8.2 ng/mL having > 30% inhibition of platelet deposition, with near complete inhibition of fibrin and platelet deposition at 72 ng/mL. Betrixaban did not cause significant effects on standard coagulation (PT or aPTT) or template bleed time measurements at

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were submitted.

Safety pharmacology programme

A number of *in vitro* safety pharmacology studies and 4 *in vivo* safety pharmacology studies were submitted in order to assess effects on respiratory, CNS, and cardiovascular systems.

In an in vivo respiratory safety pharmacology study (NC-05-0015) in male Sprague Dawley rats at doses up 1,000 mg/kg, no adverse effects on the respiratory system were noted.

A summary of the main findings from the CNS safety pharmacology study is presented in **Table 7**.

Table 2. Summary of CNS system safety pharmacology study with betrixaban

Type of study (ID) – GLP status	Test system, study design	Results
General and neurobehavioral activity study (NC-05-0028) GLP: yes	• Species: rat (SD), 8F/group • Route: oral gavage • Doses: 0, 100, 300, 1000 mg/kg • Duration: single dose • Endpoints: clinical observations, BW, FOB once prior to treatment and 1, 3, and 6 hours following treatment (qualitative and quantitative assessments), motor activity (assessments performed after FOB)	**<u>1000:</u>** • ↓activity and arousal for up to 3 hours post-dose • ↓palpebral closure, ↓respiratory rate with effects on breathing pattern, salivation, muzzle or urinary staining at 1 and/or 3 hours • ↓body temperature at all time-points post-dose

The effect of betrixaban on ion channels was studied in cells transfected to expressing the hERG channel or in canine cardiomyocytes. Results from these studies are summarised in **Table 8**.

Table 3. Summary of studies investigating the effect of betrixaban & metabolites on cardiac ionic currents

Ionic current	Test-article	Test system, concentrations, study ID | GLP status	Results
IK_r	Betrixaban	• HEK293 cells • 1.03, 3.22, 11.2, 34.5, 54.4 µM • NC-08-0220 | GLP: yes	≥11.2 µM: inhibition of hERG current density at a frequency of 1 Hz. IC_{50} = 31.9 µM
		• HEK293 cells • 0.85, 1.7, 8.2, 25.6 µM • NC-06-0039 |GLP: no	≥8.2 µM: inhibition of hERG current density at a frequency of 2 Hz IC_{50} = 16.5 µM
		• HEK293 cells • 0.032, 0.1, 0.316, 1, 3.162, 10 µM • NC-08-0177 | GLP: no	Inhibition of hERG current IC_{50} = 9 µM
		• CHO cells • 0.29, 1.1, 3.0, 10 µM • NC-10-0370 | GLP: no	≥0.29 µM: inhibition of hERG current IC_{50}=1.8 µM (IC_{20}=0.48 µM)
	PRT062802 (N,N-dimethyl-4-carboxybenzamidine)	• HEK293 cells • 1.12, 3.19, 10.8, 33.3, and 54.6 µM • NC-08-0220 | GLP: yes	≥1.12 µM: inhibition of hERG current density at a frequency of 1 Hz. IC_{50} = 44.6 µM
		• CHO cells • 31, 292 µM • NC-10-0371 | GLP: no	Inhibition of hERG current reached 8.6% and 13.3% at 31 and 292 µM, respectively. IC_{50} not determined.
	PRT054156 (N-desmethyl betrixaban)	• HEK293 cells • 1.0, 2.9, 10.0 and 27.2 µM • NC-06-0039 | GLP: no	No significant effect
	PRT058326 (O-desmethyl betrixaban)	• HEK293 cells • 0.75, 2.6, 9.9 and 33.4 µM • NC-06-0039 | GLP: no	No significant effect

Ionic current	Test-article	Test system, concentrations, study ID | GLP status	Results
IK_r and IK_s	Betrixaban	• Canine cardiomyocytes. • 25, 50, 100, 250, 500, 1000 ng/mL (0.055, 0.111, 0.221, 0.553, 1.11, 2.21 µM) • NC-08-0190 | GLP: no	• IK_s: ↑ current density amplitude at 25 and 50 ng/mL; no effect at 1000 ng/mL. The effect seen at the lower concentrations may reverse at higher concentrations. But it cannot be excluded that higher concentrations would cause further inhibition of the IKs current. • IK_r: inhibition of tail current at ≥500 ng/mL
I_{To}	Betrixaban	• Canine cardiomyocytes • 25, 250, 1000 ng/mL (0.055, 0.553, 2.21 µM) • NC-08-0191 | GLP: no	No significant effect
IK_{ur}	Betrixaban	• Canine cardiomyocytes • 25, 250, 1000 ng/mL (0.055, 0.553, 2.21 µM) • NC-08-0192 | GLP: no	No significant effect
ICa-L	Betrixaban	• Canine cardiomyocytes • 25, 250, 1000 ng/mL (0.055, 0.553, 2.21 µM) • NC-08-193 | GLP: no	≥25 ng/mL: ↓ current amplitude. When these Ca current changes were corrected for time-dependent run-down in K current, the current density was significantly decreased suggesting a direct treatment-related inhibition of the current. Amplitude of current did not return to control values upon washing betrixaban off, suggesting that effect is not reversible over the 5-min washout period. An IC_{50} value could not be determined
INa (transient & sustained)	Betrixaban	• Canine cardiomyocytes • 25, 250, 1000 ng/mL (0.055, 0.553, 2.21 µM) • NC-08-194 | GLP: no	No significant effect

The effect of betrixaban on cardiac action potential (AP) was investigated in two studies.

In the first one (NC-08-0179, non-GLP), conducted in isolated canine cardiac Purkinje fibres, betrixaban at 0.1, 1, and 5 µM prolonged the APD90 (at a basic cycle length of 2 seconds) by 6%, 22%, and 49%, respectively. Betrixaban had no statistically significant effect on resting potential, AP amplitude, or AP maximum rate of rise.

In the second study, conducted in canine ventricular strips of cardiomyocytes (NC-08-0189, non-GLP), betrixaban at the doses tested (between 50 and 1500 ng/mL) did not cause statistically significant changes in the resting membrane potential, the amplitude of the Phase 0 upstroke, or the maximal rate of depolarization of the canine myocardial cellular strips. There was a trend towards a concentration-dependent lengthening of the APD which was more pronounced at 90% repolarization than at 60% and at 30% repolarization.

To evaluate the impact of betrixaban on BP, HR and ECG parameters, two in vivo studies were conducted a single oral dosing study in telemetered dogs, and one in anaesthetised rats and are summarised in **Table 9**.

Pharmacodynamic drug interactions

The potential pharmacodynamic interaction of betrixaban with a p-gp inhibitor was investigated in Male Beagle dogs (Study NC-06-0040, Non-GLP). Co-administration of betrixaban (3 mg/kg) with verapamil (10 mg/kg) showed no additive increase in the hypotension or heart rate changes, compared with dogs administered verapamil.

Table 4. *In vitro safety* pharmacology studies performed with betrixaban

Type of study, study number	Test system/ Test condition	Results
In vivo Cardiovascular Dog telemetry NC-08-0163 GLP	Dog/ Beagle 2M, 2F/group Single oral dosing (gavage) 3, 15, 75 mg/kg	• The 3 mg/kg dose of betrixaban did not elicit changes in heart rate and blood pressure or changes in QT, RR, and QTcV intervals compared to the vehicle controls. • The 15 and 75 mg/kg doses of betrixaban elicited a dose dependent increase in heart rate (increase of 36-59% (32-51 bpm)) that lasted for up to six and 18 hours post-dosing ($p<0.05$), respectively. • The 15 mg/kg dose of betrixaban did not elicit changes in systolic, diastolic and mean BP, while a transient decrease in mean BP was observed at the 75 mg/kg dose (13% decrease, $p< 0.05$). • Betrixaban at 15 and 75 mg/kg elicited a dose-related and statistically significant ($p < 0.05$) prolongation of the QTcV interval for up to 11 and 12 hours, respectively, following dosing when compared to vehicle-treated animals. • The 15 and 75 mg/kg doses of betrixaban elicited peak prolongation times of 37 msec (16% increase at 2 hours post-dose) and 49 msec (20% increase at 1 hour post-dose), respectively. • The mean male and female Cmax and $AUC_{(0-\infty)}$ exposure at 3 mg/kg was inferred from study NC-05-0038 and was 160 (male) and 196 ng/mL (female), and 968 (male) and 1,653 (female) ng*hr/mL, respectively.
In vivo Cardiovascular Anaesthetised Rat NC-08-0180 Non-GLP	Male Rat/ Sprague-Dawley N=4/group Intravenous, IV, infusion for 1 hour: 10, 30 mg/kg	• The 10 mg/kg/hr betrixaban did not have any effect on the measured CV parameters (HR, BP, ECG). The plasma concentration in these animals at the end of infusion was ~3 5 µM. • All rats infused 30 mg/kg/hr died before the end of the hour long infusion with plasma concentration at or above 10 µM.

2.3.3. Pharmacokinetics

The non-clinical pharmacokinetics of betrixaban was evaluated in a series of in vitro and in vivo studies conducted in mice, rats, dogs and Cynomolgus monkeys. Rat and dog were used as the main toxicology species.

Absorption

PK parameters after single oral or IV administration of betrixaban are summarised in **Figure 4**.

Figure 2. Summary of intravenous and oral betrixaban pharmacokinetics in mouse, rat, dog, and monkey

	Mouse	Rat	Rat	Rat	Dog	Dog	Monkey	Monkey
Route	IV	IV	PO	PO	IV	PO	IV	PO
Study	NC-14-0590	NC-10-0327	NC-10-0327	NC-10-0327	NC-10-0328	NC-10-0328	NC-10-0329	NC-10-0329
Dose (mg/kg)	2	1	5	30	0.5	2.5	0.75	7.5
C_{max} (ng/mL)	368	279	88.0	1,281	200	98.4	753	552
T_{max} (hours)	NA	NA	2.25	2.05	NA	0.938	NA	2.2
$AUC_{0-\infty}$ (ng*hr/mL)	483	383	456	5,387	317	825	716	4,180
CL (mL/min/kg)	69	43.6	NA	NA	26.5	NA	18.7	NA
V_{ss} (L/kg)	13.2	32.9	NA	NA	48.8	NA	13.40	NA
$T_{1/2}$ (hours)	2.6	8.75	11.9	5.07	21.2	13.1	9.56	12.3
F (%)	NA	NA	23.8	46.9	NA	51.6	NA	48.7

After oral administration, betrixaban was rapidly absorbed with a Tmax that ranged from 1 hour (dog) and 2 hours (rat and monkey) post dose followed by a biphasic decline with an apparent terminal t1/2 ranging from 3h (mice) to 8-10h (rat, monkey) and 21h in dogs. In IV studies, betrixaban exhibited a biphasic decline with a terminal half-life of approximately 3 hours in mice, 8 to 12 hours in rat and monkey, and 21 hours in dogs.

The effect of food on oral bioavailability of betrixaban was investigated in female dogs administered a single 30 mg/kg dose under both fed and fasted conditions in a crossover design followed by a 2-week washout period. When administered in a fed state, exposure, as assessed by both Cmax and AUC was reduced by approximately 30% as compared to the fasting state (study NC-15-0603).

Distribution

- **Protein binding**

Plasma protein binding of betrixaban was evaluated in plasma of various species at concentration levels of 60-70 ng/mL. The percentage of betrixaban that was protein bound in rat, dog, monkey, and human plasma was 65.7%, 59.2%, 58.4% and 61.1%, respectively (study no. NC-10-0330).

- **Distribution in blood**

The Blood/Plasma concentration ratios were 1.74 in rat, 1.98 in dog, and ranged between 1.26 and 1.4 in human blood (study no. NC-10-0331).

- **Tissue and organ distribution**

Tissue distribution was investigated in male albino (SD) and pigmented (Long Evans) rats administered a single 30 mg/kg dose of [^{14}C]-betrixaban (study no. NC-06-0074).

In albino rats, the highest concentration observed in blood and plasma occurred at 4 hours post dose and was below the lower limit of quantitation by 24 hours post dose. The highest concentrations were also observed at 4 hours post dose (in 25 out of 38 tissues) or 8 hours post dose (9 of 38 tissues). The highest concentrations of radioactivity were found in the liver, renal medulla, renal cortex, and urinary bladder at 4 hours post dose, which reflected excretion of parent compound or metabolites.

The maximum concentrations in most tissues in pigmented rats were observed at 24 hours post dose (first time point evaluated). The highest concentrations were measured in the uveal tract of the eye, the pituitary gland, lachrymal gland-exorbital, and lachrymal gland-intraorbital. There was no radioactivity associated with the brain or spinal cord in this study.

The elimination of drug-derived radioactivity from the testes and uveal tract of the eye in pigmented animals was slow and incomplete at 672 hours post dose.

Metabolism

In the clinical [14C] mass balance study (06-005; 07-012) two major metabolites were identified. One of these major metabolites identified, PRT062802, was a direct product of the amide hydrolysis. The second major metabolite, PRT063069, was a sulphated conjugate derived from the other portion of betrixaban liberated via the initial amide hydrolysis.

In the 26-week study in rats (NC-07-0085) the concentrations of both PRT062802 and PRT063069 at the NOAEL (150 mg/kg) were > 20 fold higher than the therapeutic concentrations observed in humans at the 80 mg betrixaban dose.

Excretion

Mass balance data was obtained from rat (study NC-10-0332, -38), dog (study NC-10-0333), monkeys (study NC-10-0334) and in human (06-005) and are summarised in **Table 10**.

Table 5. Excretion of radioactivity (% of dose) in rat, dog and monkey after administration of ^{14}C-betrixaban

Species	Dose (mg/kg)	Route	Urine	Faeces	Bile	Recovery	Time
Rat (male) NC-10-0338	1	iv	22.6	81.3	NA	107	48 h
Rat (male, bile duct cannulated) NC-10-0332	25 200	oral repeat dosing 7x	24.4 18.9	43.3 53.0	21.9 9.9	92.8 85.0	72 h
Dog (male, bile duct cannulated) NC-10-0333	3.0 15	oral repeat dosing	11.7 14.0	14.4 16.2	54.4 60.7	81.4 93.4	72 h 192 h bile 96h
Monkeys (male, bile duct	5	oral repeat dosing	5.9	49.1	31.4	90.1	192 h bile

cannulated) NC-10-0334							96h
Human 06-005	40 mg	oral single dose	11	85	NA	96	

Pharmacokinetic drug interactions

In a study in dogs (NC-14-0589), betrixaban was co-administered with verapamil, a P-gp inhibitor, and dose-normalised exposure increased 70% compared to betrixaban alone.

In human liver microsome studies, betrixaban, at concentrations up to 10 µM, caused less than 50% inhibition of the metabolism of the probe substrates at concentrations of up to 10 µM. Results from this study indicated that betrixaban did not inhibit CYP isozymes 1A2, 2C9, 2C19, 2D6, or 3A4/5 (IC50 >10 µM) (study no.NC-07-0107).

A CYP induction study was conducted to evaluate the ability of betrixaban to increase the expression and activity of CYP1A2, 2B6, and 3A4. The results demonstrated that incubation of betrixaban at concentrations of up to 10 µM with cryopreserved hepatocytes increased neither expression nor activity of these CYPs (study no.NC-16-0726).

2.3.4. Toxicology

Single dose toxicity

A summary of the single-dose toxicity studies submitted is presented in **Table 11**.

Table 6. Summary of single-dose toxicity studies with betrixaban

Study ID/GLP	Species/ Sex/Number/ Group	Dose (mg/kg)/Route	Observed max non-lethal dose/lethal dose	Major findings
NC-08-0181/non-GLP	Rat/5F	1000/oral	1000/NA	No findings
NC-05-0029/GLP	Rat/5F, 5M	500, 1000, 2000/oral	500/500	Deaths were recorded in each dose group on either Study Day 2 or 7, with laboured respiration and gasping occurring in those animals.

NC-05-0013/GLP	Dog/4F, 4M	10, 30, 100, 300	100/300	One female dog died of haemoperitoneum one day after dosing 300 mg/kg. Microscopic findings included: periductal mixed-cell inflammation, hepatocellular necrosis, and/or subcapsular haemorrhage in the liver; mixed-cell inflammation and/or haemorrhage in the gall bladder; tubular nephropathy in the kidney; and atrophy, lymphoid necrosis, and/or haemorrhage in the thymus. Prothrombin time and activated partial thromboplastin times were prolonged for all doses beginning with a slight increase on Study Day 2

Repeat dose toxicity

A summary of non-pivotal, non GLP repeat dose toxicity studies with betrixaban are presented in **Table 12**.

Table 7. Non pivotal repeat-dose toxicity studies

Study ID	Species/Sex/ Number/Group	Dose (mg/kg)/Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
NC-07-0123	Mouse/21M	200, 400, 600	12 days	200	Mice had minimal to moderate renal tubular epithelial degeneration or intratubular crystal formation at 400 and 600 mg/kg and hepatic changes of bile duct hyperplasia and microvesicular hepatocellular degeneration.
NC-08-0183	Rat/2F, 2M	1000	5 days	<1000	On Study Day 6, one male rat was found dead, with the cause of death presumed to be test article related.
NC-08-0182	Rat/5F, 5M	30, 100, 300	7 days	300	Under the conditions of this study, betrixaban produced no evidence of toxicity based on extensive laboratory evaluations. Dosages of 100 and 300 mg/kg were associated with prolongation of rothrombin time in both males and females. Dosages of 300 mg/kg appeared to increase uine output.
NC-08-0184	Dog/2F	3, 10, 30	7 days	10	Prolonged bleeding was observed at the 10 and 30 mg/kg dose groups. The increased occurrence of emesis in the 30 mg/kg/day dose group may indicate a dose limiting toxicity for high levels of sustained anticoagulation in female beagle dogs.

Repeat dose GLP oral toxicity studies were performed in rats dosed for 14 days, 90 days and 26 weeks (6 months), and in dogs dosed for 14 days, 90 days, and 39 weeks (9 months). Findings are summarized in **Table 13**.

Table 8. Summary of pivotal repeat dose toxicity studies with betrixaban

Species/ strain **Study no.** **GLP status**	**Duration** **Dose** (mg/kg/d) **Route**	**NOAEL** (mg/kg/d)	**Major findings**
Rat/ SD – Main: 10/sex/grp – Recovery: 5/sex (C, HD) – TK: 9/sex (LD, MD, HD) NC-05-0037 GLP: yes	14 days + 14 days recovery 0, 50, 200, 600 Oral gavage	200	Mortality – 600: 1F (TK) on D8 (dehydrated, GI tract distension), 1M on recovery D2 (thin, weak, dehydrated, cold-to-touch, lack of righting reflex, small thymus and spleen) Clinical signs, BW, FC – ≥200: salivation – 600: thinness, weakness, dehydration, ↓activity, ↓faeces, breathing changes in F (laboured, abnormal sounds), red fur staining, ↓BW and BWG Clinical pathology – ≥50: presence of green crystals in urine – ≥200: ↑PT, ↑P – 600: ↑aPTT, ↑fibrinogen, ↑WBC, ↑neutro., ↑ALT, ↑total bilirubin, ↑creatinine, ↑BUN, ↑glucose, ↓K, ↓Cl, ↑urine volume – At recovery (600): P, bilirubin (F), BUN (M), glucose (F) changes still observed Histopathology – Bone marrow: hematopoietic hypocellularity, myeloid hypercellularity, myeloid hyperplasia (1F), necrosis (600) – Kidney: inflammation and tubular dilatation with intratubular/ductal crystalline material (600) – Lungs: organized haemorrhage (600: 1F) – Thymus/ LN/ spleen: lymphoid necrosis/ atrophy (600) – At recovery (600): renal changes observed in 1/4 surviving M
Rat/ SD – Main: 15/sex/grp – Recovery: 6/sex (C, HD) – TK: 9/sex (LD, MD, HD) NC-06-0046 GLP: yes	90 days + 4 weeks recovery* 0, 50, 200, 400 Oral gavage	50	Mortality – 200: 1F - due to tracheal necrosis with obstruction of lumen by a fibrin plug – ≥200: 5M at 200 mg/kg & 9M+2F at 400 mg/kg - due to subacute nephropathy and associated renal azotemia in most animals, with additional pharmacologic haemorrhage in 1M/group ⇒ dosing terminated on D42 at 400 mg/kg* Clinical signs, BW, FC – ≥200: salivation (post-dosing and occasionally pre-dose), prominent backbone, thin body, dehydration, hunched posture, red fur staining – 400: fecal output, ↓BW, ↓FC Hematology – ≥200: ↑PT, ↑neutro. (M), ↑LUC – 400: ↑aPTT, ↓RBC, ↓Ht, ↓Hb, ↑RDW (F), ↑retic. (F), ↑WBC, ↑neutro., ↓lymph., ↑mono., ↓eosino., ↑baso., ↑PLT, ↑MPV (M) – At recovery (400): ↓RBC, ↓Hb, ↑RDW Biochemistry – ≥200: ↑BUN, ↑creatinine, electrolyte changes in M (↑Ca, ↑P, ↑Na) – 400: ↑AST (M), ↑ALT, ↓bilirubin, ↑glucose, ↑cholesterol (M), ↓TG, ↓total protein, ↓A:G (↓albumin, ↑globulin), electrolyte changes (↓Ca, ↑P,

Species/ strain **Study no.** **GLP status**	**Duration** **Dose** (mg/kg/d) **Route**	**NOAEL** (mg/kg/d)	**Major findings**
			↓Na in F, ↓K, ↓Cl) – <u>At recovery (400):</u> ↑BUN and creatinine (M), ↓bilirubin <u>Urinalysis</u> – ≥200: ↑volume, ↓specific gravity, turbid appearance, presence of crystals (calcium sulfate, ammonium urate, bilirubin crystals in M, tyrosine crystals in F) <u>Histopathology</u> – Bone marrow: ↑M:E ratio and hypocellularity (M≥200; F: 400) – Glandular stomach: ulceration (M: 400) – Kidney: subacute nephropathy (≥200) – Liver: degeneration/necrosis of biliary epithelium (≥200 in M, 400 in F) – Skeletal muscle: myofiber necrosis (≥200) – Trachea: epithelial necrosis / hyperplasia (≥200) – Thymus, LN, spleen: lymphoid atrophy/ necrosis (≥200) – considered as stress-related – Adrenals: cortical hypetrophy, single-cell cortical necrosis (≥200) – considered as stress-related – Misc: foci of haemorrhage in adrenal, brain, cecum, epididymis, heart, lung, lymph nodes, rectum, stomach and thymus – <u>At recovery (400):</u> kidney (chronic nephropathy), liver (biliary hyperplasia), skeletal muscle (regeneration)
Rat/ SD – Main: 10/sex/grp – Recovery: 5/sex (C, HD) – TK: 9/sex (LD, MD, HD) NC-07-0085 GLP: yes	26 weeks + 4 weeks recovery 0, 10, 40, 150 Oral gavage	~~150~~ 40	<u>Clinical pathology</u> – ≥40: ↑PT – 150: ↑aPTT, ↑(minimal) BUN & creatinine in M, ↓K in M, ↓Cl. – <u>At recovery (150):</u> ↑CK (x3.0) <u>Histopathology</u> – Kidney: dilatation of the distal convoluted tubules and/or collecting ducts and ↑intravascular leukocytes (M:150)
Dog/ Beagle – Main: 3/sex/grp – Recovery: 3/sex (C, HD) NC-05-0038 GLP: yes	14 days + 14 days recovery 0, 3, 15, 75 Oral gavage	3	<u>Mortality</u> – 75: 2F euthanized on D1&7 – changes in respiratory rate, and/or labored breathing. Cause of poor/deteriorating condition not established for D1 animal; for D7 animal, pharmacological effect was a contributing factor (multiple sites of haemorrhage: thymus, pericardium, thorax, skeletal muscle). <u>Clinical signs, BW, FC</u> – 75: salivation mostly for up to 2h post-dosing with associated wet fur, vomiting, trembling, ↓activity, ↓BW, ↓FC <u>Electrocardiography</u> – ≥15: ↑HR <u>Hematology</u> – ≥15: ↑PT, ↑aPTT – 75: ↓RBC parameters in M (RBC, Hb, Hct, retic.), ↑WBC, ↑neutro., ↑mono., ↑fibrinogen – <u>At recovery (75):</u> ↓RBC w/ ↑retic. in M, ↓Hb, ↓Hct <u>Biochemistry</u> – 75: ↑ALT (x6.7-7.5), ↑AST (x2-2.5), ↑ALP (x2.6-

Species/ strain **Study no.** **GLP status**	**Duration** **Dose** (mg/kg/d) **Route**	**NOAEL** (mg/kg/d)	**Major findings**
			3.9), ↑GGT (x2.9-3.6) – <u>At recovery (75):</u> ↑ALP (x1.2-1.6), ↑GGT in M (x1.4) <u>Urinalysis</u> – 75: turbid appearance <u>Histopathology</u> – Gall Bladder: inflammation, hypertrophy/ hyperplasia (75) – Kidney: tubular dilation, tubular degeneration, interstitial inflammation, transitional hyperplasia sometimes associated with mineralization (75) – Liver: inflammation/fibrosis of large bile ducts, periportal/ perivenous inflammation (M:75; F≥15), hypertrophy/hyperplasia of large bile ducts, hepatocellular degeneration/necrosis (75) – Thymus, LN, spleen, GALT: lymphoid atrophy (75) – considered as stress-related – Misc: haemorrhages in various organs (incl lungs, LN, adrenals, aorta, esophagus, fat, skeletal muscle, pericardium, trachea) – <u>At recovery (75):</u> gallbladder (epithelial hyperplasia), liver (inflammation/fibrosis of large bile ducts, biliary hyperplasia/hypertrophy); severity of changes was decreased indicating partial recovery
Dog/ Beagle – Main: 4/sex/grp – Recovery: 2/sex (C, MD, HD) NC-05-0006 GLP: yes	90 days + 28 days recovery 0, 3, 10, 30 Oral gavage	3	<u>Clinical signs</u> – Salivation, vomiting <u>Electrocardiography</u> – ≥10: ↑(dose-related) QT/QTc <u>Clinical pathology</u> – ≥10: ↑PT, ↓RBC parameters in F (RBC, Hb, Hct) – 30: ↑aPTT <u>Histopathology</u> – Liver: mixed cell inflammation in the periductal connective tissue of bile ducts (30)
Dog/ Beagle – Main: 3/sex/grp – Recovery: 2/sex (C, HD) NC-07-0095 GLP: yes	39 weeks + 4 weeks recovery 0, 3, 10, 30 Oral gavage	~~30~~ 10	<u>Mortality</u> – 30: 1M found dead on D188 –cause of death not determined but not considered test article-related as no adverse clinical signs or anatomic pathology changes were noted <u>Clinical pathology</u> – 30: ↑PT, ↑aPTT <u>Histopathology</u> – 30: ↓vacuolation of tubular epithelium in F, segmental tubular regeneration (1/3 F)

Genotoxicity

Betrixaban was evaluated for potential genotoxicity by an in vitro bacterial reverse mutation assay, an in vitro Chinese hamster ovary cell chromosome aberration assay, and in an in vivo rat micronucleus assay (summarised in **Table 14**). None of these studies indicated that betrixaban may be genotoxic or clastogenic.

Table 9. Summary of betrixaban genotoxicity studies

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria/NC-08-0185/GLP	Salmonella strains TA908, TA100, TA1535, TA1537 and E. coli strains WP2 uvrA	2.5-5000 ug/plate, +/- S9	Negative
Gene mutations in mammalian cells/NC-08-187/GLP	CHO-cells	0.625-20 ug/plate, +/- S9	Equivocal: The percentage of cells with structural aberrations was significantly increased above that of the solvent control at dose level 20 µg/mL in the non-activated 20-hour exposure group ($p < 0.05$). However, the percentage of cells with structural aberrations in the betrixaban-treated group (5.5%) was within the historic solvent control range (0.0-5.5%). Therefore, the statistical finding at 20 µg/mL dose level is not considered to be biologically relevant.
Chromosomal aberrations in vivo/NC-08-0188/GLP	Rat, micronuclei in bone marrow, 5/sex/grp	500, 1000, 2000 mg/kg	Negative

Carcinogenicity

Carcinogenicity studies were not submitted as patients will not be dosed for longer than 6 months.

Reproduction Toxicity

The pivotal reproductive and developmental toxicity studies are summarised in **Table 15**.

Table 10. Summary of reproductive and developmental toxicology studies with betrixaban

Study type **Species** **Study no.**	**Route** **Doses** (mg/kg/d) **Duration**	**NOAEL** (mg/kg/d)	**Major findings**
FEED Rat (22/sex/gp) NC-07-0096	Oral (gavage) 0, 10, 40, 150 M: 28d premating to termination F: 14d premating to GD7 (C-section GD13)	Fertility: 150 Early embryonic development: 150	- Alopecia of paw/forelimb (M, ≥40), oral discharge (M, 150) - ↓BW/BWG (M, 150), ↓ (6%) FC (M, 150)
EFD Rat (25F/gp) NC-06-0072	Oral (gavage) 0, 20, 50, 200 GD7-17 (C-section GD21)	Maternal: 50 Developmental: 200	F0 Dams - 1F euthanized on GD18 due to adverse clinical condition (200) - Excess salivation (200) - ↓BWG, ↓FC (200)
EFD Rabbit (20F/gp) NC-06-0073	Oral (gavage) 0, 15, 45, 150 GD7-19 (C-section GD29)	Maternal: 15 Developmental: 45	F0 Dams - Mortality due to adverse clinical condition (≥45) ⇒ early termination of the 150 mg/kg dose group on GD18/20/21 - Scant feces (≥15), red substance in cage (pan), red/yellow perivaginal substance, no feces, pale extremities, ↓motor activity (150) - Necropsy findings associated with apparent haemorrhaging in lungs (≥45), thymus, uterus, vagina, thoracic cavity, trachea, esophagus, heart, kidney, liver (150) - BW loss (150), ↓BWG (45), ↓FC (≥45)
PPND Rat NC-14-0593	Oral (gavage) 0, 20, 50, 200 GD7-PND20	Maternal: 50 Developmental: 50 F1 growth & reproduction: 200	F0 Dams - Mortality on GD21 – 1found dead, 1 euthanized due to adverse clinical observations (200) - Red/ brown perivaginal substance, rales (200) - ↓ gestation BWG and FC (200) F1 pre-weaning - ↑ no. stillborn pups and no. of litters with stillborn pups (200 - 5 pups in 4 litters)

Toxicokinetic data

Toxicokinetic data were obtained in single and repeat dose toxicity studies, and from a number of genotoxicity and reproduction toxicity studies conducted with betrixaban, and are summarised in **Table 16**.

Table 11. Animal-to-human exposure ratios from the betrixaban toxicology studies

Study No./ Species	**Doses** [a] (mg/kg)	**Duration of Dosing**	**NOAEL AUC_{0-24}** (ng*hr/mL)	**Multiple** [b]	**NOAEL C_{max}** (ng/mL)	**Multiple** [b]
Patients	80 mg/day	35-42 days	AUC_{0-24} = 425	NA	C_{max} = 36	NA
Single-dose						
NC-05-0013 /Dog	10, 30, 100, 300	1day	99,571	234x	7,449	207x
Repeat-dose						
NC-08-0182 /Rat	30, 100, 300	7 days	36,535	86x	2,783	77x
NC-05-0037 /Rat	50, 200, 600	14 days	22,708	53x	1,784	50x
NC-06-0046 /Rat	50, 200, 400	90 days	13,040	31x	2,344	65x
NC-07-0085 /Rat	10, 40, 150	6 months	40,059	94x	3,662	102x
NC-08-0184 /Dog	3, 10, 30	7 days	5,281	12x	1,050	29x
NC-05-0038 /Dog	3, 15, 75	14 days	768	1.8x	115	3.2x
NC-05-0006 /Dog	3, 10, 30	90 days	1,373	3.2x	193	5.4x
NC-07-0095 /Dog	3, 10, 30	9 months	27,178 (4,003 [c])	64x (9.4x)	2,951 (567 [c])	82x (15.8x)
Gentoxicity						
NC-08-0188/Rat[d]	500, 1000, 2000	24/48h	58642	137x	4183	116x
Reprotoxicity						
NC-07-0096/Rat	10, 40, 150[g]	Males 10 weeks, females 14d premating until GD7	27946	65x	2450	68x
NC-06-0072/Rat	20, 50[h], 200[i]	GD 7-17	4409/18752	10/44x	710/1560	20/43x
NC-06-0073/Rabbit	15[e], 45[f], 150	GD 7-19	2679/15008	6.2/35x	1106/4837	30/134
NC-14-0593/Rat[m]	20, 50[j], 200[k]	GD 7-20	4409/18752	10/44x	710/1560	20/43x

Local Tolerance

Local tolerance studies were submitted but are not relevant to this application, as betrixaban is intended for oral administration.

Other toxicity studies

Renal Crystal Investigation

The applicant submitted an investigational study in rats to determine the identity of crystals that were present within the renal tubule lumens and were associated with tubular epithelial injury. Data from this study showed that the crystalline material within the lumens of proximal convoluted tubule was compatible with betrixaban and not the O-desmethyl metabolite of betrixaban.

Phototoxicity

An *in vivo* phototoxicity study in the pigmented male Long-Evans rat was performed by dosing rats with either vehicle alone; 400, 600, or 1,000 mg/kg/day betrixaban; or 8-methoxypsoralen (8-MOP) as a positive control for 2 days (study no.NC-08-0166). Rats were then exposed to simulated daylight and the tissues from betrixaban-dosed rats were compared to those obtained from rats dosed the positive control compound, 8-MOP. There was no indication that betrixaban is associated with a risk for causing phototoxic injury to human patients.

Metabolites

Samples from chronic repeat dose toxicity GLP studies in rat (NC-07-0085) and dog (NC-07-0095) were tested for their levels of the two major betrixaban metabolites, PRT062802 and PRT063069 and compared to exposures observed in humans (**Table 17**).

Table 12. Pharmacokinetic parameters of betrixaban metabolites at steady state from chronic toxicology studies in rat and dog in comparison to steady-state exposure in healthy subjects following therapeutic dose or a single supra-therapeutic oral dose

PRT062802

Dog (9-month Tox, Week 39)				Rat (6-month Tox, Week 26)				Clinical Study			
Dose (mg/kg)	Gender	Cmax (ng/mL)	AUC(0-24) (ng·hr/mL)	Dose (mg/kg)	Gender	Cmax (ng/mL)	AUC(0-24) (ng·hr/mL)	Study	Cmax (ng/mL)	AUC(0-24) (ng·hr/mL)	%AUC* 62802/betrix
3	Male	BLQ	BLQ	10	Male	12.5	51.3	**Study 08-014**	7.33 ± 2.90	66.0 ± 18.1	17.7 ± 5.14
	Female	BLQ	BLQ		Female	13.7	50.0	**80 mg QD, Day 7****			
10	Male	2.32 ± 1.21	25.8 ± 11.6	40	Male	51.3	351	**Study 07-013**			
	Female	1.05 ± 0.32	12.4 ± 4.02		Female	50.6	323	**140 mg Single Dose**			
								Male	8.03 ± 4.52	97.1 ± 41.2***	22.0 ± 7.55
30	Male	5.98 ± 3.53	84.8 ± 42.2	150	Male	178	2066	**Female**	7.60 ± 3.43	127 ± 53.1***	18.8 ± 6.51
	Female	7.15 ± 2.63	119 ± 51.5		Female	168	1983				

PRT063069

Dog (9-month Tox, Week 39)				Rat (6-month Tox, Week 26)				Clinical Study			
Dose (mg/kg)	Gender	Cmax (ng/mL)	AUC(0-24) (ng·hr/mL)	Dose (mg/kg)	Gender	Cmax (ng/mL)	AUC(0-24) (ng·hr/mL)	Study	Cmax (ng/mL)	AUC(0-24) (ng·hr/mL)	%AUC* 63069/betrix
3	Male	BLQ	BLQ	10	Male	14.4	45.8	**Study 08-014**	19.9 ± 6.23	103 ± 29.1	14.8 ± 6.33
	Female	BLQ	BLQ		Female	39.2	91.5	**80 mg QD, Day 7****			
10	Male	2.35 ± 0.85	19.1 ± 7.31	40	Male	69.4	405	**Study 07-013**			
	Female	1.44 ± 0.56	13.7 ± 4.07		Female	178	605	**140 mg Single Dose**			
								Male	14.4 ± 6.86	127 ± 62.0***	15.7 ± 7.30
30	Male	8.34 ± 4.34	60.1 ± 30.9	150	Male	260	2307	**Female**	28.1 ± 12.9	242 ± 151***	18.8 ± 11.4
	Female	9.97 ± 6.78	98.6 ± 54.3		Female	321	2785				

*%AUC = $[AUC(0\text{-}24)_{metabolite} / AUC(0\text{-}24)_{betrix}] / [MW_{metabolite} / MW_{betrix}] * 100$

** Data at steady-state on Day 7

*** AUC(0-∞) following a single oral dose of 140 mg

BLQ= data were below limit of quantification

QD = Daily

Since amide hydrolysis is more prevalent in S9 fractions than in microsomes, the in vitro metabolism of betrixaban was investigated notably in rat and human liver S9 fractions (study no.NC-10-0336). In S9 extracts from both species, PRT062802 and PRT062803 were identified in the S9 extracts in the presence of NADPH. Approximately 2-4% of betrixaban converted to PRT062802 after incubation with rat induced S9.

To further assess the mutagenic potential of major human metabolites, GLP-compliant Ames tests were run for PRT062802, PRT063069, and ACM benzamide (PRT062803).

Tester strains were exposed to vehicle alone and different concentrations of test article. There was no test article related toxicity in any of the tester strains with or without exogenous metabolic activation. All the test article concentrations were non-toxic. There was no significant increase in the number of revertants in the test article treated plates.

The test articles were evaluated as negative (non-mutagenic) under the conditions of this study.

Impurities

Nonclinical 14-day to 9-month repeat dose toxicology studies were used to qualify related substances present in betrixaban. Two lots of betrixaban were used in all the chronic rat and dog studies. For the assessment, the lot with the highest level of each related substance was used to determine the qualified level for that related substance. The proposed related substance acceptance criteria for each related substance is less than the lowest concentration qualified for 7 of the 12 related substances, and are less than the greatest concentrations qualified for 3 of the remaining 5 when using the conservative dog multiples. All betrixaban related substances were qualified based on the most sensitive species (dog) margins at the NOAEL dose and exposure of betrixaban, except for 2 substances which were not required to be qualified, and were easily qualified with the NOAEL margins of the rat studies.

An assessment of potentially genotoxic, mutagenic and carcinogenic related substances was performed using a combination of in silico analysis and bacterial mutagenesis assays. In vitro analysis revealed that none of these substances were genotoxic in Ames test and many of them were not at all detected after synthesis.

2.3.5. Ecotoxicity/environmental risk assessment

Table 13. Summary of main study results

Substance: Betrixaban			
CAS-number: 330942-05-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	KOAWIN v1.10	3.86	<4.5 threshold
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0813	μg/L	>0.01 threshold

2.3.6. Discussion on non-clinical aspects

Pharmacology

The potency, kinetics and selectivity of betrixaban as a fXa inhibitor were determined in purified enzyme assay systems. Betrixaban inhibited free human coagulation factor Xa with IC50 of ~ 1.2 nM and Ki of 117 pM. Betrixaban inhibition was highly selective for fXa over other serine proteases.

In addition, betrixaban was shown to inhibit human fXa in its most active form, within the prothrombinase complex on the surface of activated platelets, in a non-competitive manner with a Ki of 801 pM. In kinetic experiments, the human fXa/ Betrixaban inhibitor complex dissociated at a slow rate with an off rate (koff) of 0.02 s-1.

The potency of prothrombinase inhibition by betrixaban, measured as the concentration to achieve a 2-fold increase in the lag time, was 90 nM in human whole blood and 360 nM in plasma, respectively.

The effect of betrixaban on clotting assay parameters (prothrombin time [PT] and activated partial thromboplastin time [aPTT]) was assessed in plasma and whole blood systems. Betrixaban was approximately 4-fold more potent in clotting inhibition in human blood as compared to rabbit (IC50 ~200 ng/mL in human blood vs. ~800 ng/mL in rabbit blood).

Betrixaban demonstrated low or no effect on agonist (e.g. ADP or PAF) induced platelet aggregation in human plasma (IC50 ≥ 8 μM), indicating that it does not affect platelet aggregation.

The antithrombotic activity of betrixaban was further investigated in a number of different animal models.

Betrixaban treatment resulted in dose-dependent reduction of clot formation in a rabbit DVT model (minimum effective plasma concentration of 1.75 μM at 3 mg/kg) and inhibition of thrombosis formation as well as reduced biomarkers of thrombotic activity (e.g. F1+2, TAT, and TF-induced thrombin generation) in the expansion chamber in the arteriovenous (AV) shunt model in baboons (0.05 – 0.48 mg/kg, effective plasma concentrations: 8 – 72 ng/mL, IV), without significant effects on standard coagulation markers (PT or aPTT) or template bleed time measurements.

The effect of Betrixaban on arterial thrombosis was investigated in a chemical damage-induced ferric chloride ($FeCl_3$) model in the rat. Intravenous administration of Betrixaban (0.2 – 2 mg/kg, IV) dose-dependently reduced the incidence of and increased the time to carotid artery occlusion in the rat model at doses above 0.7 mg/kg (Cplasma ≥ 0.2 μM).

The anti-haemostatic effects after Betrixaban treatment were evaluated in different bleeding models including mouse (tail transection blood loss, 1-6 mg/kg, IV), rabbits (cuticle bleeding time, 1 -3 mg/kg, Cave = 0.63 μM, IV), rhesus monkeys (template bleed time, 4- 7.5 mg/kg, Cave = 0.5μM, PO), and baboons (TBT, 0.05-0.48 mg/kg, Cplasma = 72 ng/mL, IV). Betrixaban caused no or minimal prolongation of bleeding times but increased blood loss at doses that were effective in these animal thrombosis models with exposure margins of 2-8 fold compared to the anticipated clinical exposure.

In vitro pharmacology studies showed that Betrixaban inhibits hERG in transfected cells with an IC50 that ranged from 1.8 to 31.9 μM (814 to14,418 ng/mL, i.e. 22x clinical exposures).

Studies in vivo in the rat did not reveal any effects on CNS or respiratory functions (after a single oral gavage administration of Betrixaban with estimated Cmax at NOAEL of ≥ 3082 ng/mL (i.e. 38x clinical exposures).

In vivo cardiac safety pharmacology (telemetry) studies in dogs (3, 15, 75 mg/kg, PO) demonstrated a dose-dependent and significant prolongation of QT (mean increases of 27 and 31 msec) and in QTcV (mean increases of 37 and 49 msec) in the 15 and 75 mg/kg groups, respectively. Additionally, there were significant and dose-dependent increases in heart rate and a decrease in mean blood pressure. The estimated NOAEL for the adverse cardiovascular effects (QT and QTc prolongation) was 3 mg/kg with estimated Cmax levels of 160 - 196 ng/mL in males and females, respectively (i.e. ~ 5x margins to clinical exposures).

A dedicated thorough QT study (07-013), was performed in healthy volunteers treated at up to 140 mg; the outcome was considered to be negative, (see also clinical aspects section of this report). Thus, the cardiovascular side effects observed in dogs should not be a concern for use in humans and from a non-clinical perspective, no further action was considered necessary.

A drug interaction study with the calcium channel blocker verapamil was conducted in dogs to assess effects on cardiovascular function. In telemeterised dogs, betrixaban at exposure levels 2- to 4-fold above maximally expected human therapeutic concentrations did not affect the inhibitory cardiovascular effects of verapamil as compared to administration of verapamil alone.

Pharmacokinetics

Betrixaban was rapidly absorbed after a single oral dose, with T_{max} ranging from 1 to 2 h in the plasma of mice, rats, dogs and monkeys, which is similar to Tmax in humans (2 h at 80 mg oral dose). Oral bioavailability was low to moderate in rat (24-47%), moderate in monkey (49%) and moderate to high in dog (52-75%). A moderate bioavailability (~38 %) was observed in humans. In non-clinical species as well as in humans the oral bioavailability was found to be dose-dependent. Betrixaban exhibited nonlinearity in exposure, with greater than proportional increases in exposure levels with increasing dose up to 15 mg/kg. At doses higher than 20 mg/kg, less than proportional increases were observed in rats. The non-linearity of the PK profile of betrixaban may be due to combinations of different factors, including potentially decreased clearance and/or increased absorption.

Betrixaban showed moderate to high plasma clearance in the rats (43.6 mL/min/kg), dog (26.5 mL/min/kg), and monkey (18.7 mL/min/kg) following intravenous dosing and the volume of distribution (Vd) was large (13-49 L/kg) in all species, indicating a large extravascular compartment.

Food intake decreased the exposure of betrixaban in animals by 30-50% as assessed by both Cmax and AUC0-∞, relative to fasted animals. An increased exposure to betrixaban in fasting patients may therefore result in an increased risk of bleeding in those patients.

Radiolabelled betrixaban was widely distributed into tissues except for the CNS and was rapidly eliminated from most tissues. In albino rats, the highest concentrations of radioactivity in blood and plasma as well as in the liver, renal medulla and cortex of the kidney, and urinary bladder were found at 4 hours post dose, which in turn reflected excretion of drug or radiolabelled metabolites, and most radiolabel was BLQ by 24 hours. The majority of the administered radiolabelled compound, 80%, was recovered in faeces and 20% in urine.

In the pigmented rats the highest concentrations were observed at 24 hours post dose (first time point studied), with the highest concentrations detected in the uveal tract of the eye, pituitary gland, lachrymal gland-exorbital, and lachrymal gland intraorbital. The elimination from tissues in pigmented rats was slower, likely due to melanin binding. Most of the administered radioactivity was excreted by 48 hours post dose. However, in the uveal tract of the eye and from the testis, radioactivity was still measurable after 672 h (the last time-point analysed). Given the lack of ocular adverse effects in the non-clinical studies (see Toxicology) or in clinical studies, the binding of betrixaban to melanin does not appear to be associated with any obvious risk for ocular toxicity in patients.

The transfer of betrixaban and/or metabolites across the placenta has not been specifically evaluated. However, the reproductive toxicity studies suggest that betrixaban administration did not interfere with fertility, prenatal or postnatal development, including maternal function at doses of up to 45 mg/kg that resulted in exposure margins up to 200 fold compared to that observed in humans at the 80 mg dose.

A metabolic stability study indicated that the predominant metabolites identified in vitro were derived from CYP-independent hydrolysis. The primary metabolic pathway in man is amidolysis in which betrixaban is cleaved yielding the two major human metabolites PRT062802 and PRT063069. At steady state, the human plasma AUC of PRT062802 was approximately 18% that of betrixaban, while the AUC of PRT063069 was approximately 15% that of betrixaban.

In all species, drug-related radioactivity was excreted in bile and in urine mainly as unchanged parent drug. The extent of biliary excretion was much higher in dogs (60%), than in monkeys (30%) and rats (10-20%); this translates into higher Cmax- and AUC-based bile-to-plasma ratios in dogs (700 to 2000) than in monkeys (700-900) and rats (40-125). The bile was the primary route of excretion in dogs and monkeys; in rats, the urinary route of excretion was of similarly or even highly involved (19-25%).In dogs and monkeys, the urinary route of excretion was minor (12-14% and 6%, respectively).

Excretion of betrixaban and/or metabolites into milk was not specifically evaluated. However, in the reproductive toxicity study, betrixaban treatment did not have an obvious effect on the F1 generation pups that may have been exposed to the drug during maternal gestation (via placental transfer) or via maternal milk during the lactation period.

When co-administered with the potent P-gp inhibitor verapamil, betrixaban (a P-gp substrate) exposure was increased approximately 2-fold in dogs, indicating that dose-adjustments may be required in patients with concomitant use of betrixaban with P-gp inhibitors.

Toxicology

The macroscopic and microscopic evaluation of both rats and dogs show that the main organs affected by betrixaban are the liver and kidneys. In the rat dilatation of distal convoluted tubules and/or collecting ducts and increased intravascular leukocytes were observed at 150 mg/kg/day in the 26 week study and in the 13 week study subacute nephropathy was observed at ≥200 mg/kg/day. These doses correspond to 94 and 88 times the clinical exposure and the exposure margins to the corresponding NOEALs in these studies are 20 and 30 times the clinical exposure, respectively. Similarly the findings in the dog were seen in animals exposed more than 60 times the intended clinical exposure (corresponding to 9.4 times the clinical exposure to NOEAL).

The liver of exposed rats and dogs displayed degeneration/necrosis, peri-portal necrosis, minor reactive changes to sinusoidal lining cells, minimal to moderate inflammation of the portal spaces and minimal to slight hyperplasia/hypertrophy of the biliary ducts, gall bladder inflammation, hyperplasia/hypertrophy and minimal to moderate inflammation of the portal spaces. In the rats, the effects were seen only with the high betrixaban dose but not with lower doses (≤ 150 mg/kg/day). Hepatic changes observed in dogs were mild to moderate in severity with a time-dependent partial recovery seen after 14 days post-treatment and a complete resolution after a 28-day recovery period.

Additional clinical signs of toxicity included decreased food consumption, body weight and general signs of malaise like decreased activity, thin body, hunched posture and vomiting. However, these symptoms did appear at supra-therapeutic human exposures (>50 times the human exposure to NOEAL based on AUC).

Clinical chemical parameters were affected in both rat and dog. These include changes in urinary factors, AST, ALT, albumin, albumin/globulin ratio among others in the mid- and high-dose groups.

Overall, considering the margin of exposure of the observed effects, these are considered be of little relevance for humans. Furthermore, there was no sign of a cardiovascular effect in humans or of betrixaban-induced liver injury, neither in healthy volunteers nor in the phase III study.

Betrixaban was not found to be genotoxic or clastogenic in vitro or in a rat study in which the animals, at 2000 m/kg, were exposed 112 and 114 times the human exposure based on AUC and Cmax, respectively.

The applicant did not submit any carcinogenicity studies since patients will not be exposed for longer than 6 months. This was considered acceptable.

Betrixaban was not found to be teratogenic in rat and rabbit embryofoetal toxicity studies, nor did it have an effect in female or male fertility, or postnatal development of developing rats. In general the exposure margins to the embryofoetal NOAELs in these studies were >35 times the human exposure.

Juvenile toxicity studies were not submitted by the applicant as these are not considered necessary for the intended adult indication.

Betrixaban was found to have low risk of phototoxicity, as the data generated in this study did not show any signs of skin or eye phototoxicity.

The human metabolites are considered qualified from a non-clinical standpoint since the exposure of the metabolites, PRT062802 and PRT063069, at the lowest NOAEL in the rat toxicology studies (50 mg/kg/day) was approximately 30-fold above those concentrations anticipated in patients at the 80 mg dose. In addition, in vitro these major metabolites are inactive on human fXa activity.

ERA

Based on the PECSurface Water estimate, a Phase II environmental risk analysis would be required to determine whether betrixaban poses a potential risk to the environment.

Moreover, the log Dow for the drug substance was calculated using KOAWIN v1.10 and not through experimental testing. Since betrixaban is an ionisable molecule, phase I PBT screening should have been performed based on either log Dow values determined at a least 3 pH values ranging from pH 5 to 9, or on an ion-corrected log Dow value. Depending on these estimates it may be necessary to conduct a Fish bioaccumulation test.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical pharmacology data package supports the rationale to use betrixaban in the intended indication.

The non-clinical pharmacokinetic profile of betrixaban is considered to have been adequately characterised.

Non-clinical data did not reveal any special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, toxicity to reproduction, and development. Cardiovascular safety pharmacology studies in dogs indicated that betrixaban has the potential to prolong the QT interval. The clinical relevance of this finding is however unlikely, as the thorough QT study in humans was negative and there was no signal of potential cardiotoxicity observed in the Phase III clinical study.

The risk of betrixaban to the environment requires further characterisation through additional environmental risk assessment studies.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

Betrixaban Clinical Pharmacology Studies

Study	Study Title	Objective
PN002	A 4-Period, Open-Label, Randomised, Crossover Study to Investigate the PK and PD of Betrixaban and Other Oral Anticoagulants in Healthy Male Subjects	Comparison of PK and PD of betrixaban to other oral anticoagulants (dabigatran and rivaroxaban)
PN009	3-Period, Randomised, Crossover Study to Investigate the PK and PD of Betrixaban and Other Oral Anticoagulants in Healthy Male and Female Subjects	Compare PD parameters for betrixaban, dabigatran etexilate, and rivaroxaban
06-005	An Open-Label, Single-Dose, Mass-Balance Study to Assess the Disposition of ^{14}C-Labeled PRT054021 in Healthy Male Subjects	Mass Balance Study
07-013	A Double-Blind Randomised Single Dose Crossover Trial to Define the ECG Effects of Betrixaban (PRT054021 and Formerly MLN1021) Using a Clinical and a Supratherapeutic Dose Compared to Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women: a Thorough ECG Trial	Thorough QT Study
07-008	The Effect of a Proton Pump Inhibitor or an Antacid on the PK Properties of a Solid Formulation of PRT054021 Administered to Healthy Subjects as a Single Dose	Drug Interaction Study
07-009	A Phase I Study to Investigate the Effects of Ketoconazole on the PK of PRT054021 in Healthy Subjects	Drug Interaction Study
08-014	A Phase I Study of the Safety and PK of Betrixaban and Digoxin at Steady-State in Healthy Subjects	Drug Interaction Study
PN010	A Study to Evaluate the Effect of Verapamil on the PK of Betrixaban in Healthy Subjects	Drug Interaction Study
08-016	PK, PD, and Tolerability of Betrixaban Administered Orally in Subjects with Normal and Reduced Renal Function.	Renal Impairment Study
PN003	A Single and Multiple Dose Study to Assess the Safety, Tolerability, and PK of Betrixaban in Japanese	Ethnic Sensitivity Study to compare PK and safety in Japanese and non-Japanese subjects

Phase 2 Studies with PK/PD and Preliminary Efficacy Data

Study	Study Title	Objective
PN006	A Phase II, Open-Label, Dose Exposure Confirmation Study to Evaluate the Pharmacokinetics and Safety and Tolerability of Betrixaban (MK-4448) in Adult Patients with Non-Valvular Atrial Fibrillation or Atrial Flutter (DEC)	Phase 2 dose-finding
05-003	Evaluation of the Factor Xa Inhibitor, PRT054021, Against Enoxaparin in a Randomised Trial for the Prevention of Venous Thromboembolic Events After Unilateral Total Knee Replacement (EXPERT)	Phase 2 dose-finding
08-015	A Phase 2, Randomised, Parallel Group, Dose-finding, Multicentre, Multinational Study of the Safety, Tolerability and Pilot Efficacy of Three Blinded Doses of the Oral Factor Xa Inhibitor Betrixaban Compared with Open-label Dose Adjusted Warfarin (EXPLORE)	Phase 2 dose-finding

Phase 3 Pivotal Study

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s)	Dosage Regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Study
11-019 (APEX)	• Demonstrate, in defined study cohorts, the superiority of extended duration (35 Days + 7 day window, i.e., 35-42 Days allowed) anticoagulation with betrixaban as compared to the standard of care (10 ± 4 Days) with enoxaparin for prevention of VTE in patients who are at risk due to acute medical illness	Double-blind, randomized, double-dummy, parallel group	40 or 20 mg SQ QD for 10 ± 4 Days with betrixaban placebo for 35 Days (+ 7 day window) 80 or 40 mg PO QD for 35 Days (+ 7 day window) with enoxaparin placebo SQ QD for 10 ± 4 Days	Betrixaban doses 80 or 40 mg Based on Renal Function and P-gp inhibitor Oral daily dosing for 35 Days	7513	Subjects enrolled will have been admitted to the hospital with one of five diagnoses documented to be associated with excess risk of VTE: acutely decompensated heart failure, acute respiratory failure, acute infection, acute rheumatic disease and acute ischemic stroke. Subjects had at least one of eligibility risk factors: Age ≥ 75 years; Age 60 – 74 years: D-dimer ≥ 2 x ULN; Age 40 – 59 years: D-dimer ≥ 2 x ULN and History of VTE or History of Cancer; Immobility of ≥ 24 hours observed or anticipated Severe Immobility, and observed or anticipated Severe or Moderate Immobility ≥ 3 additional days; and bed rest and hospitalized for at least 3 Days.	Each patient will be enrolled in the study for 65 Days (up to a maximum of 77 Days) unless additional safety follow-up is required due to ongoing events.

2.4.2. Pharmacokinetics

The PK of Betrixaban has been investigated in vivo in 10 biopharmaceutical studies, 10 clinical pharmacology and 12 in vitro studies. Population (POP) PK and PK/PD analyses were also conducted based on a Phase 2 study (08-015) and the pivotal Phase 3 study (APEX).

In the Phase 2 studies and the single Phase 3 study, the immediate release capsule formulation intended for commercial manufacturing was used.

Absorption

Study 07-012 (PPL-1121):

This was an open-label, single oral and single intravenous dose study in a target population of 8 healthy male subjects aged 18–65 years. A mean absolute bioavailability of approximately 32.4% was seen in this study which was performed during fasting conditions. Significant inter-subject variation of bioavailability was evident with individual values ranging between 7.0% and 53.8%.

- **Influence of food**

The effect of food on the PK of betrixaban was evaluated in five separate studies (**Table 19**), either as a primary or secondary objective of each study. The meals were either low- or high-fat meals. The timing of the betrixaban doses ranged from as soon as 10 minutes after the meal to as long as 8 hours after the meal.

Table 14. Overview of Food Effect on Betrixaban Pharmacokinetics

Study No.	Feeding Status	Dose & Formulation	No. of Subjects **(M/F)**	Parameters **(mean [SD] or median [range])**	
				C_{max} (ng/mL)	**$AUC_{0-\infty}$** (ng*hr/mL)
04-001 [1]	Fasted	200 mg IR	9/0	119 (33.0)	2,022 (575)
	Fed	200 mg IR	9/0	111 (39.0)	1,782 (734)
05-002 [1]	Fasted	40 mg IR	10/4	10.6 (5.3)	240 (122)
	Fed	40 mg IR	10/4	3.9 (1.8)	115 (65)
09-018 [1]	Fasted	80 mg IR	11/9	75.3 (36.0)	1,338 (340)
	Fed w/ 10 minutes high-fat	80 mg IR	11/9	21.9 (21.7)	683 (497)
	Fed w/ 10 minutes low-fat	80 mg IR	11/9	38.5 (19.7)	639 (275)
	30 minutes before high-fat	80 mg IR	11/9	73.8 (54.6)	569 (154)
	2 hours after high-fat	80 mg IR	11/9	20.3 (10.5)	705 (340)
	Fasted	60 mg IR	11/9	53.4 (28.7)	893 (212)
PN001 [1]	Fasted-AM	80 mg IR	10/10	65.1 (33.2)	1,022 (467)
	Fasted-PM	80 mg IR	10/10	72.4 (34.3)	1,124 (533)
	2 hours after low-fat	80 mg IR	10/10	9.1 (7.2)	256 (137)
	4 hours after low-fat	80 mg IR	10/10	23.9 (21.0)	432 (301)
	4 hours after high-fat	80 mg IR	10/10 (-1)	52.5 (42.7)	823 (524)
	6 hours after high-fat	80 mg IR	10/10 (-1)	52.0 (33.9)	860 (528)

PN011 [1]	Fasted	90 mg IR P2	20/11	61.3 (33.8)	984 (495)
	Fed	90 mg IR P2	20/11	23.0 (17.7)	523 (232)

[1] C_{max} and $AUC_{0-\infty}$ Arithmetic mean (SD);

Distribution

The volume of distribution (V_d) in Study 07-012 was reported as approximately 32 L/kg.

- **Protein binding**

Study NC-10-0330-R0001

Plasma protein binding of betrixaban in human plasma was determined using micro-equilibrium dialysis. The percent bound of Betrixaban in human plasma was 61.1% at a concentration of 100 ng/mL.

- **Blood-plasma ratio**

Study NC-10-0331-R0001

The Blood/Plasma concentration ratio for human blood was determined for MLN1021 by analysing the radioactive content of 14C-MLN1021 in whole blood, plasma, and blood cells.

The Blood/Plasma concentration ratios ranged between 1.26 and 1.4 in human blood.

Elimination

Based on study 07-012 (i.v. betrixaban), mean betrixaban total CL and CL_R were 677 ml/min and 159 mL/min, respectively. The terminal elimination half life was reported as approximately 30-40 hours across studies.

- **Excretion**

Study: 06-005

This was an open-label, single-dose, mass-balance study conducted in 5 healthy male subjects.

Each subject received a single oral 40 mg dose of PRT054021 (maleate salt) drug substance labelled with 14C carbamimidoyl.

Based on data from the mass balance study and the absolute bioavailability study, biliary elimination of unchanged drug was deemed to be the major elimination pathway (ca. 50%) and metabolism is a minor elimination pathway (20-25 %). Furthermore, renal excretion of unchanged drug is a minor elimination pathway (20-25 %).

Urine data from several other PK studies support this conclusion where fraction excreted as unchanged drug is reported to be in the range of 5 %. Further, renal clearance of Betrixaban is reported as 159 mL/min based on study 07-012 while filtration (fu*GFR) is expected to be about 50 ml/min.

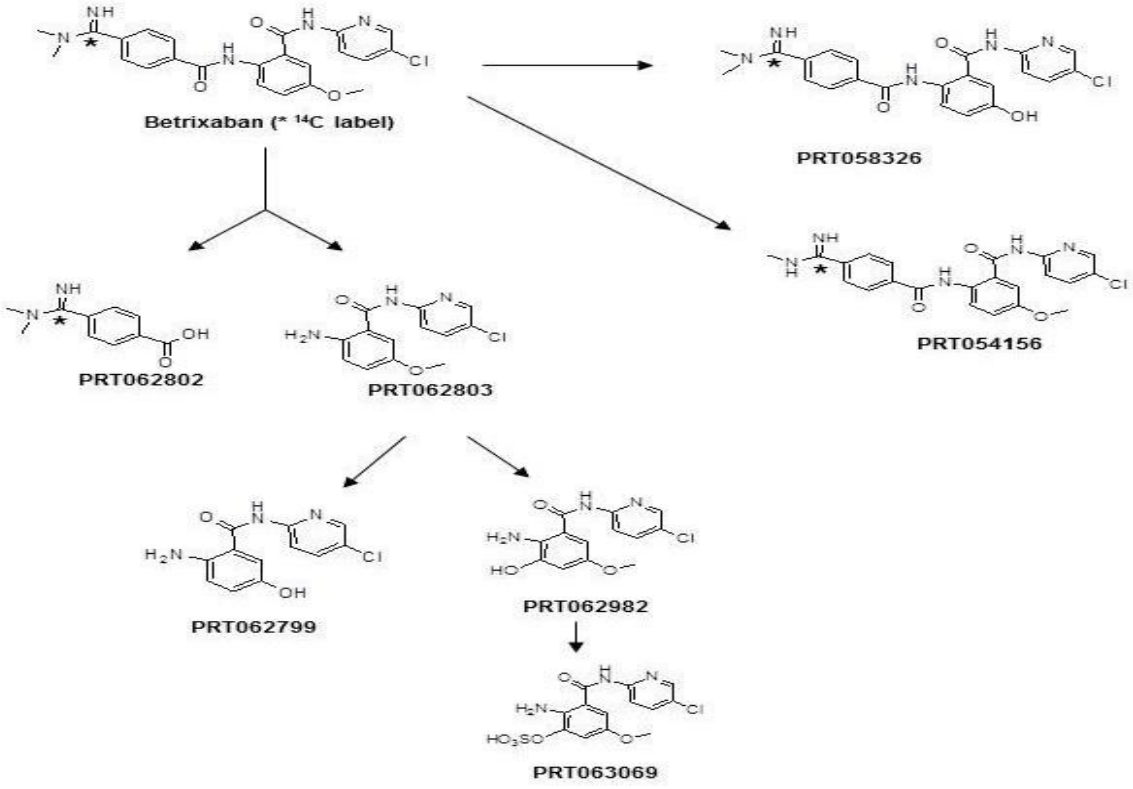
- **Metabolism**

Two inactive, major (> 10% of the betrixaban AUC) polar metabolites have been identified in human plasma): a hydrolysis product (N,N-dimethyl-4- carboxybenzamidine or PRT062802 (M5)), and a Phase II sulphate conjugate (2-amino-3- [5-chloropyridin-2-yl carbamoyl]-5-methoxyphenyl hydrogen sulphate or PRT063069).

At steady-state, the plasma AUC of PRT062802 is approximately 18% that of betrixaban, while the AUC of PRT063069 is approximately 15%. Both PRT062802 and PRT063069 are inactive (IC50 for fXa inhibition > 10 μM) and do not inhibit hERG (IC50 > 40 μM). Other minor metabolites (e.g., O-desmethyl and N-desmethyl betrixaban) have been identified, with estimated AUC of less than 1% that of betrixaban.

The proposed metabolic pathways for betrixaban is summarised in the below figure.

Figure 3. Metabolic pathways of betrixaban



Based on data from studies performed during fed conditions, the inter-individual variability in AUC is approximately 40-70 %. Based on data from study 15-020, intra individual variability in AUC is approximately 20-25 %. This figure is however likely higher during fed conditions.

The two major circulating human metabolites, PRT062802 and PRT063069, were both quantified in additional clinical and nonclinical studies (See also non-clinical section of this Report).

Additional pharmacology studies were conducted to determine if these metabolites posed a safety concern. Betrixaban and the two major metabolites were tested in the Factor Xa chromogenic assay to determine their activity against the target (**Table 20**).

Table 15. Factor X_a inhibition by betrixaban and major metabolites

Inhibition in FXa Chromogenic Assay (n=5) ±SD		
Compound	Conc. (µM)	Inhibition (%)
Betrixaban	0.01	89.2 ± 0.9
PRT062802	10	17.7 ± 3.5
PRT063069	10	15.1 ± 4.4

- **Pharmacokinetic data analysis**

Pharmacokinetic data was also analysed in population pharmacokinetic analyses from the APEX study.

One PK sample per patient was collected at the day of discharge (Visit 2), but no later than Day 14 after randomisation. Of 3,293 samples (patients) available, 144 concentration values were not quantified, and 3 other samples which occurred more than 14 days after randomisation were excluded from analysis.

Due to the very limited PK information in the APEX study, no conclusions on betrixaban PK should be made on the basis the population PK analysis.

Dose proportionality and time dependencies

- **Dose proportionality**

Study PN003

An exploratory analysis was conducted to preliminarily assess dose proportionality of betrixaban AUC0-inf, AUClast, and Cmax. The analysis model included ln(dose) as a covariate and subject as a random effect. The estimated slope of the ln(dose) and 90% confidence interval are summarised in **Table 21**.

Table 16. Dose proportionality assessment of betrixaban in Study PN003

Parameter	Estimated Mean Slope	Model CV% a	df	90% CI
Cmax [ln(ng/mL)]	1.95	57.0	7	(1.47, 2.43)
AUC0-24 hr [ln(ng*hr/mL)]	1.76	25.4	7	(1.50, 2.02)
AUC 0-inf [ln(ng*hr/mL)]	1.74	25.5	7	(1.48, 1.99)

Source: Table 14.2.5.1

CI = confidence interval; df = degrees of freedom; ln = natural logarithm

a Percent coefficient of variation (CV%) was estimated as 100xsqrt(exp(s2) - 1), where s2 is the residual variance from the linear mixed effect model.

Study 04-001

This was a single centre, double-blind, randomized, placebo-controlled, multiple dose study of PRT054021 (40 mg, 80 and 120 mg), moxifloxacin (400 mg) or placebo (4:1:1 ratio). A greater than dose-proportional increase in systemic exposure to betrixaban is seen in the clinically relevant dose range. On average, for a doubling in dose, systemic exposure to betrixaban at steady state would be predicted to increase approximately 2.6-fold.

- **Time dependency**

Not studied. However a visual inspection of Ctrough data from study 08-014 did not indicate time varying PK.

Special populations

	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	297/1253	246/1253	45/1253

- **Impaired renal function**

Study 08-016

This was a single centre, open-label, parallel group study in subjects with normal renal function and subjects with varying degrees of impaired renal function. Subjects were enrolled into 1 of 4 renal function groups (normal, mild impairment, moderate impairment or severe impairment) according to the estimated glomerular filtration rate (eGFR) determined at screening, using the simplified 4-variable Modified Diet in Renal Disease Study Group (MDRD) equation. Results from this study are summarised in **Table 22**.

Table 17. Summary of statistical analysis of AUC_{0-24} and C_{max} following administration of 80 mg of betrixaban in healthy subjects or subjects with varying degrees of renal impairment

Parameter	Day	Mild Renal Impairment versus Healthy Subjects Ratio (90% CI)	Moderate Renal Impairment versus Healthy Subjects Ratio (90% CI)	Severe Renal Impairment versus Healthy Subjects Ratio (90% CI)	Severe Renal Impairment versus Mild Renal Impairment Subjects Ratio (90% CI)
Subjects grouped using 186 as multiplier in the MDRD equation:					
AUC_{0-24}	1	1.54 (0.963, 2.47)	1.90 (1.20, 3.01)	2.46 (1.60, 3.80)	1.60 (1.02, 2.50)
AUC_{0-24}	8	1.89 (1.18, 3.03)	2.27 (1.43, 3.59)	2.63 (1.71, 4.06)	1.39 (0.888, 2.18)
C_{max}	1	1.70 (0.952, 3.02)	2.27 (1.29, 3.99)	2.54 (1.49, 4.33)	1.50 (0.863, 2.60)
C_{max}	8	1.88 (1.05, 3.35)	2.32 (1.32, 4.07)	2.52 (1.48, 4.29)	1.34 (0.772, 2.32)
Geometric least squares mean ratios (90% CI)					

- **Impaired hepatic function**

No dedicated hepatic impairment study was submitted.

- **Gender, race and weight**

Based on a rather large study, comprising 48 healthy men and 48 healthy women, a difference between males and females was seen where AUC was approximately 35 % greater in females than in males.

No information is currently available regarding the influence of race or weight given the limitations in the population PK analysis.

Pharmacokinetic interaction studies

- **In vitro**

CYP inhibition

Study NC07-0107-R0001

CYP inhibition potential of PRT054021 at concentrations up to 100 mM was evaluated in human liver microsomes with or without 30 minute pre-incubation of PRT054021.

Results from the competitive and time-dependent inhibition studies showed that PRT054021 had IC50 > 80 mM for CYP1A2, 2C9, 2D6 and 3A4. IC50 for 2C19 were 43 and 88 mM for competitive and time-dependent inhibition, respectively.

Study NC-16-0722-R0001

The objective of this study was to evaluate the potential of MLN1021 to inhibit the major human cytochrome P450 (CYP) isozymes up to a concentration of 10 μM.

Results from this study indicated that MLN1021 did not inhibit CYP isozymes 1A2, 2C9, 2C19, 2D6, or 3A4/5 (IC50 > 10 μM).

CYP induction

Study NC-16-0726-R0001

The objective of this study was to investigate the potential of betrixaban to induce CYP1A2, CYP2B6 and CYP3A4 using an mRNA endpoint across three donors in cryopreserved human hepatocytes. The study was negative for the induction of systemically expressed 1A2 and 2B6, but positive for induction of intestinal CYP3A4.

Transport proteins

Study NC-16-0735:

This study evaluated the transport mechanisms of MLN1021 using the Caco-2 cell monolayer system in the absence or presence of efflux pump inhibitors, MK571 (for MRP2), GF120918 (for both P-gp and BCRP) and cyclosporine (CsA, for both MRP2 and P-gp). Results indicated that betrixaban is a potential substrate of MRP2 and P-gp and/or BCRP.

Study NC-09-0282-R0001

The purpose of this study was to provide data on the interaction of PRT054021 with the ABC (efflux) transporters: human P-gp (ABCB1/MDR1), human MRP2 (ABCC2), human BCRP (ABCG2/MXR) and BSEP (ABCB11/sP-gp), and with human uptake transporters OATP1B1 (OATP2, OATP-C), OATP1B3 (OATP8) and OAT1.

The study results demonstrated that betrixaban inhibited both Pgp and BCRP, both with IC50 values of 11.6 μM. Betrixaban demonstrated no interaction with MRP2, BSEP, OAT1, OATP1B1 or OATP1B3 in the clinically relevant concentration range.

Study 07-009

This was a single-center, open-label, randomized sequence, 2-way crossover study of a single dose of PRT054021 administered to 12 healthy subjects on 2 occasions, once alone and once following 5 days of ketoconazole 200 mg administered orally every 12 hours. Results are summarized in **Table 23**.

Table 18. Summary of mean (SD) PK parameters in Study 07-009

Parameter (unit)	PRT054021 Alone (n=11)	PRT054021 with Ketoconazole (n=12)
C_{max} (ng/mL)	13.01 (9.16)	28.57 (20.44)
AUC(0-∞) (ng*h/mL)	195.4 (96.2)	395.3 (139.5)
T_{max} (h) [a]	1 (0.5-6.0)	1 (0.5-6.02)
t1/2 (h) [a]	34.5 (29.02-48.73)	25.76 (21.13-32.89)
CL/F (L/h)	276.7 (180.3)	115.9 (49.4)
Vz/F (L)	14730 (10143)	4398 (1994)

Notes: SD=standard deviation.

Study PN010:

This was an open-label, 2-period, fixed-sequence study to evaluate the influence of multiple oral doses of verapamil on the single dose PK of betrixaban. Mean betrixaban Cmax, and AUC increased by approximately 5- and 3-fold, respectively, when coadministered with both single dose and multiple dose verapamil.

Study 08-014:

This was a single-center, open-label, sequence-randomized, 3-period crossover study of betrixaban and digoxin, where each drug was administered alone and in combination for 7 days to 18 healthy subjects. No clinically relevant interaction was seen between betrixaban and digoxin.

Study 07-008

This was a single-center, open-label, 3-period crossover, period randomized study of a single 40-mg dose of betrixaban administered orally to healthy subjects. The 40-mg capsule was administered on 3 occasions: once by itself, once after 5 days of pre-treatment with a proton pump inhibitor (esomeprazole [Nexium Delayed-Release capsule, 40 mg, once daily]) and once after the administration of aluminum hydroxide/magnesium hydroxide antacid (Maalox Extra Strength, 5 mL). No clinically relevant interaction was seen between betrixaban and a PPI (esomeprazole) or an antacid (aluminium/magnesium hydroxide).

2.4.3. Pharmacodynamics

Mechanism of action

Betrixaban is a potent benzamidine-based small molecule inhibitor of human plasma-derived factor Xa (fXa) that inhibits fXa in its physiologic form, within the prothrombinase complex on the surface of activated platelets. The prothrombinase complex (fXa in combination with factor Va) catalyzes the formation of thrombin from prothrombin. This process is part of the coagulation cascade and inhibition of fXa results in anticoagulation.

Preliminary characterisation of betrixaban was conducted in *in vitro* assays, and is described in the non-clinical section of this report.

Primary pharmacology

Two phase I studies in healthy subjects compared the PK/PD of betrixaban with that of other anticoagulants in order to determine the likely therapeutic dose of betrixaban. One study (PN002) evaluated the PK/PD after single doses of betrixaban, rivaroxaban and dabigatran, in the fasted state. The second study (PN009) evaluated repeat doses of betrixaban, rivaroxaban or dabigatran all in the fed state. One additional study (08-016) in renally impaired patients and normal subjects provides supportive PK/PD data of betrixaban following multiple doses in the fasted state. The design of these studies is briefly presented below before the presentation of the global PD results.

- Study PN002: This was a 4-period, single-blind, placebo-controlled, randomised, crossover study to investigate the PK and PD of single oral doses of betrixaban and 2 other anticoagulants (dabigatran and rivaroxaban), in 20 healthy men. After an overnight fast, subjects were administered single doses of betrixaban 120 mg, dabigatran 150 mg, rivaroxaban 20 mg, or placebo.
- Study PN009: This was a 3-period, open-label, partially randomised, crossover study to investigate the PK and PD of multiple-oral doses of betrixaban and other anticoagulants (dabigatran and rivaroxaban) in healthy men and women. In the first 2 periods, subjects received dabigatran 110 mg BID for 4 days, and rivaroxaban 20 mg QD for 4 days in a randomised manner. In Period 3, all subjects received betrixaban 60 mg QD for 7 days in a fixed sequence.
- Study 08-016: The effect of renal impairment on betrixaban PK/PD following single or multiple day QD dosing with 80 mg betrixaban in the fasted state was determined in this parallel group study in 32 subjects (8 patients in each group classified as normal, mild, moderate, or severe renal impairment).

The Phase 2 studies, EXPERT and EXPLORE Xa also provided key PK/PD data used to facilitate the final dose selection for the Phase 3 study, APEX. In EXPERT, 15 mg and 40 mg BID doses of betrixaban were administered to patients undergoing unilateral knee replacement. In EXPLORE Xa, once daily doses of 40, 60, and 80 mg were evaluated in patients with documented non-valvular atrial fibrillation (AF).

No PD results were provided from the Phase 3, APEX study.

Effect on anti-Xa activity

In study 08-016, maximum plasma concentrations of betrixaban that occurred at a median tmax of 1 to 3 hours postdose on Day 8 across all renal function groups corresponded with the time of maximum increased anti-fXa activity. At steady state, betrixaban demonstrated an increase in anti-fXa activity, to maximum values at 3 hours postdose (0.27 to 0.77 IU/mL), and then declined gradually, remaining quantifiable for the renal impairment groups at 48 hours postdose, but being below the limit of quantification for the subjects with normal renal function. The anti-fXa activity following betrixaban was higher in subjects with renal impairment and increased with the degree of renal impairment, with the individual data at 2 to 48 hours postdose showing moderate correlations. There was a trend for an increase in anti-fXa activity with increasing plasma concentrations of betrixaban.

In EXPERT, the 40 mg BID gave results for anti-fXa activity similar to enoxaparin while the 15 mg BID dose produced a lower effect. In EXPLORE Xa, anti-fXa activity increased with increasing betrixaban dose, suggesting the possibility of a relationship between these PD and PK parameters.

Effect on Clotting Time Assessments (aPTT, INR, PT)

In study 08-016, maximum plasma concentrations of betrixaban that occurred at a median tmax of 1 to 3 hours postdose on Day 8 across all renal function groups corresponded with the time of maximal changes in the coagulation parameters PT, aPTT and INR. The effects on betrixaban on the decrease in PT and increases in aPTT and INR were apparent across all renal function groups, but generally occurred to a greater extent in the moderate and severe renally impaired subjects.

No other relevant data on PT and aPTT were provided.

Effect on Thrombin Generation (TG)

Estimation of the EC50 for TGI could not be performed in PN002 study. In PN009 study, since the 60 mg dose of betrixaban was administered in a fed state, drug exposure was lower than expected from other PK studies in healthy subjects, which were performed in a fasted state. Due to the low exposure (betrixaban median C24h = 3.2 ng/mL), sufficient data were not available to do appropriate PK/PD correlation necessary to calculate the IC50 for TGI. Therefore, these data were not used for constructing the model for dose selection of patients with acute medical illnesses.

Nonetheless, in these 2 studies, there was a direct positive correlation between the plasma concentrations of the anticoagulants and the %TGI. Maximal PD effects were generally observed around the time of anticoagulant Cmax.

TG was inhibited by > 80% with betrixaban and rivaroxaban and by > 60% with dabigatran.

In study 08-016, maximum plasma concentrations of betrixaban that occurred at a median tmax of 1 to 3 hours postdose on Day 8 across all renal function groups corresponded with the time of maximum reduced TG. At steady-state, betrixaban demonstrated a reduction of TG, compared to Day 1 pre-dose (from approximately 12000 to 5000 RFU at the lowest levels 2 hours post dose on Day 8) which was independent of renal function. The level of reduction was generally sustained over the following 3 and 4-hour postdose assessments. Overall the data were highly variable and individual TG values versus eGFR at 2 to 48 hours postdose generally showed no correlation. There was, however, a trend for a decrease in TG with increasing plasma concentrations of betrixaban.

In EXPERT, the 15 mg BID betrixaban dose had TG similar to enoxaparin while the 40 mg BID betrixaban dose a higher level. In EXPLORE Xa, TG exhibited a dose-response relationship in betrixaban-treated patients, with lowest levels in the 80 mg group and highest in the 40 mg group.

Effect on D-dimer

In EXPLORE Xa, median increase from baseline in D-dimer concentrations was higher in the betrixaban 40 mg group, less high with 60 mg betrixaban or unchanged with 80 mg betrixaban.

Effect on Platelet Aggregation

Betrixaban has no direct effect on platelet aggregation (NC-15-0712).

Effect on Bleeding Time

No relevant data on bleeding time were provided by the Applicant.

Secondary pharmacodynamics

Cardiac safety: In the first-in-human study (02-401), single oral betrixaban doses of 5 to 550 mg were administered in 59 healthy men (another 20 received placebo). The increase in exposure was not proportional (clearance decreased with increasing dose). The half-life was approximately 31 to 44 hours, regardless of dose. Planned PD analyses were not conducted due to the safety findings.

This study identified QT prolongation as a potential risk of betrixaban at dose levels greater than approximately 360 mg in the fasting state and at concentrations greater than approximately 250 ng/ml.

Two subjects, both males who received 550 mg dose, had clinically significant abnormalities on the ECG that were reported as AEs. In both instances, the abnormality was a prolongation of the QTcB (defined as >430 ms for males) after study drug administration. For both subjects, these prolonged QTc intervals were reported as mild in intensity and judged by the investigator to be probably related to study drug. The subjects experienced no clinical symptoms in conjunction with the ECG changes.

Study 07-013 (QT study): A thorough QT study (07-013) evaluated the proposed 80 mg therapeutic dose and a supratherapeutic dose of 140 mg both administered in the fasting state that cover the highest potential exposure levels for patients who might have higher than anticipated exposure due to concomitant P-gp inhibitor administration without dose adjustment or a limited food intake. Using the commonly accepted regulatory QT margins of an increase in QTc of no greater than 10 seconds (CHMP/ICH/2/04), there was no prolongation of QTc with betrixaban despite the fact that the average Cmax was 3-fold higher and the highest individual Cmax was 8-fold higher than the anticipated average Cmax for patients of 36 ng/mL.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Due to the limited PK sampling in the target population and the shortcomings of the population PK analysis, the results from the population PK analysis are not considered reliable. Phase 1 data has been used in order to describe all desired covariates except the influence of weight on betrixban PK where data has not been provided.

In a comparison of response rates for safety endpoints by different weight strata it is evident that patients with low body weight have a higher incidence rate of bleedings. Therefore, the SPC was revised to recommend caution when treating patient with low weight.

Across studies the absolute bioavailability was approximately 50 % lower under fed conditions. There was no clear trend as to whether a high-fat or low-fat meal had the greatest impact on betrixaban PK.

Consequently, a warning against taking betrixaban during fasting conditions, given the expected higher exposure, was proposed to be added to the SPC.

Use of betrixaban in severe renal impairment, was not recommended in the SPC given the uncertainty regarding the optimal dose in this population.

Concomitant use with P-gp inhibitors was proposed to be contraindicated due to:

1. The clinical results in the p-gp subgroup in APEX did not indicate an efficacy benefit compared to enoxaparin.
2. As only one dose level was studied in APEX, there is lacking information regarding the therapeutic window (exposure response on hard endpoints) of betrixaban. Without such information, any changes in plasma concentrations are hard to evaluate. Therefore a conservative approach was taken where we are reluctant to include scenarios in the SPC where a patient may have plasma concentrations outside normal range.
3. It has not been clarified whether the magnitude of the results in the interaction studies would have been similar if the studies were performed during fed conditions, which are the conditions recommended according to the SPC.
4. It has also not been clarified whether the betrixaban results seen in the interaction studies with ketoconazole and verapamil are possible to extrapolate to the steady state situation given the non-linear PK of betrixaban

Taken together, it is uncertain whether a patient on treatment with concomitant p-gp inhibitors will be in the normal plasma concentration range. Consequently, as a precautionary approach, concomitant treatment with P-gp inhibitors has been contraindicated. Similarly, a contraindication for p-gp inducers due to potential lack of efficacy has been included.

Lastly, as the performed mass balance study is deemed failed regarding characterization of plasma radioactivity, the lack of information regarding human major or unique metabolites according to ICH M3R(2) was further addressed during the assessment rounds. The only remaining concern for a potential poor bridge to the pre-clinical studies refers to the scenario if there is a human specific metabolite which is eliminated at a slower rate than the parent compound betrixaban and consequently may become a large metabolite in terms of exposure i.e. AUC. The risk for formation of such a metabolite, with toxic properties, is however deemed low and no further information is deemed necessary. Additional factors considered in this judgement are the limited treatment duration and the fairly large population in APEX from which there are safety data collected.

Pharmacodynamics

In vitro (non-clinical) studies, demonstrated the anticoagulant effect of betrixaban by its binding to the active site of fXa, inhibition of thrombin generation (TGI assay), effects on clotting tests PT, aPTT.

In studies PN002, PN009, 08-016, EXPERT and EXPLORE Xa, TGI exhibited a dose-response relationship in betrixaban-treated patients. Maximal reduced TG was generally observed around the time of anticoagulant Cmax.

In study 08-016, maximum plasma concentrations of betrixaban corresponded with the time of maximum increased anti-fXa activity. At steady state, betrixaban demonstrated an increase in anti-fXa activity, to maximum values at 3 hours postdose (0.27 to 0.77 IU/mL), and then declined gradually, remaining quantifiable for the renal impairment groups at 48 hours postdose, but being below the limit of quantification for the subjects with normal renal function. Maximum plasma concentrations of

betrixaban corresponded with the time of maximal changes in the coagulation parameters PT, aPTT and INR. The effects on betrixaban on the decrease in PT and increases in aPTT and INR were apparent across all renal function groups. In studies EXPLORE Xa, anti-fXa activity also increased with increasing betrixaban dose, suggesting the possibility of a relationship between these PD and PK parameters.

In EXPLORE Xa study, median increase from baseline in D-dimer concentrations seemed to be dose-related in betrixaban-treated patients. However, the relevance of these PD values is not clearly established.

PD measurements of TGI and anti-fXa activity exhibited a concentration-dependent relationship to betrixaban. However, it is not clearly established whether the correlation is linear. Furthermore, no relevant data regarding the concentration-effect relation on PT and aPTT were provided.

The exposure-efficacy analysis provided by the applicant in the PD model did not detect an exposure-response relationship to betrixaban, although a treatment effect was quantified and a lower event rate compared to enoxaparin was estimated. Significantly higher bleeding rate was estimated for betrixaban compared to enoxaparin, as well as a betrixaban concentration-safety relationship. However, the exposure-response relationships should be interpreted with caution due to the high uncertainty in the exposure predictions.

2.4.5. Conclusions on clinical pharmacology

Betrixaban has been adequately characterised from a pharmacokinetic point of view.

Betrixaban is an oral anticoagulant which inhibits human factor Xa and thereby decreases thrombin generation. These PD properties have been characterised in a number of studies in the development programme for betrixaban.

2.5. Clinical efficacy

2.5.1. Dose response studies

Three phase II dose-finding studies were submitted. These were conducted in patients with conditions other than the applied indication and are therefore presented briefly in this section.

DEC/PN006: A Phase II, Open-Label, Dose Exposure Confirmation Study to Evaluate the Pharmacokinetics and Safety and Tolerability of Betrixaban in Adult Patients with Non-Valvular Atrial Fibrillation or Atrial Flutter

This was a multicentre, open label, dose exposure confirmation study in patients with non-valvular atrial fibrillation. The primary study objective was to assess whether weight-based dosing provided equivalent twelve hour concentrations (C12h) between two different weight groups (lower weight: < 80 kg, higher weight: ≥80 kg) and reduced Betrixaban PK variability.

The study included a total of 189 patients: 74 patients were allocated to the 60 mg betrixaban (<80 kg) group, 73 patients to the 90 mg betrixaban (≥80 kg) and 42 patients to the 30 mg betrixaban (+ Amiodarone - regardless of weight) group.

Results:

The 25% lower mean concentration in the <80 kg betrixaban group compared to the group with a weight ≥80 kg indicated an overcorrection by reducing the dose by 33% from 90 mg to 60 mg in this

weight group. This dosing strategy did not achieve the C12 hr target concentration of 12.4 ng/mL, but was approximately 23% to 27% lower.

On the other hand, a dose reduction to 30 mg for patients on amiodarone resulted in statistically equivalent mean betrixaban C12 hr concentrations as patients not taking amiodarone who received a 90 mg dose.

EXPERT (05-003): Evaluation of the Factor Xa Inhibitor, PRT054021, Against Enoxaparin in a Randomised Trial for the Prevention of Venous Thromboembolic Events After Unilateral Total Knee Replacement

This was an exploratory study in which 214 patients undergoing unilateral knee replacement were randomised to receive one of two dose levels of betrixaban (15 mg or 40 mg PO BID) or enoxaparin 30 mg SC BID for 10 to 14 days for the prevention of thromboembolic events. The study was open label for randomization to enoxaparin vs. betrixaban, but the 15 mg vs. 40 mg betrixaban dose was double-blind. The randomisation ratio was 2:2:1.

The primary objectives were to provide pilot or exploratory efficacy data on betrixaban at doses of 15 mg and 40 mg PO BID compared to enoxaparin for the prevention of VTE unilateral total knee replacement, and to provide pilot data on the safety of betrixaban in the above doses and subjects. Secondary objectives included to assess the PK and PD of betrixaban at the above doses.

Results:

The results for the primary efficacy outcome are summarized in **Table 24**.

Table 19. Results for primary efficacy outcome in EXPERT study (05-003)

Parameter	PRT054021 15 mg	PRT054021 40 mg	Total PRT054021	Enoxaparin 30 mg
N with evaluable assessment*	70	65	135	40
N (%) with VTE	14 (20.0)	10 (15.4)	24 (17.8)	4 (10.0)
95% CI	11.4, 31.3	7.6, 26.5	11.7, 25.3	2.8, 23.7

* Includes those subjects with an evaluable mandatory venogram and those with a confirmed symptomatic event.

EXPLORE Xa study (08-015): A Phase 2, Randomised, Parallel Group, Dose-finding, Multicentre, Multi-national Study of the Safety, Tolerability, and Pilot Efficacy of Three Blinded Doses of the Oral Factor Xa Inhibitor Betrixaban Compared with Open-label Dose Adjusted Warfarin

This was an exploratory, randomised, parallel group, multicentre, active comparator, dose finding study of patients with documented non-valvular AF.

Its primary objective was to assess the safety and tolerability of betrixaban at doses of 40, 60, and 80 mg given orally once a day for at least 3 months compared to dose-adjusted warfarin in patients with non-valvular AF. Secondary objectives included to provide preliminary efficacy data, as well as to assess the PK and PD of betrixaban at the above doses in the target population.

A total of 508 patients were randomised to treatment groups using a dynamic randomisation to balance patients by country, concurrent aspirin use and antecedent warfarin use. The study was open label for randomisation to warfarin versus betrixaban, but the three daily dose levels of betrixaban, 40, 60, or 80 mg, were double blind. The warfarin-treated patients were managed with INR monitoring and dose-adjustments in order to maintain a target INR of 2.0 to 3.0 at maximum intervals of 4 weeks. No loading doses or dose titrations were be used for betrixaban. Each patient was treated for a minimum of 3 months; dosing continued for each patient until the last patient had reached 3 months of treatment. Importantly, patients could be enrolled into the study regardless of renal function, provided they were not undergoing dialysis; no dose adjustment was made for decreased renal function.

The primary endpoint was the occurrence of major or clinically relevant non-major bleeding. The secondary endpoints included the occurrence of any bleeding and the occurrence of death, ischaemic or non-ischaemic stroke, MI, or other systemic embolism.

Results:

Betrixaban at 40 mg was associated with less bleeding, while betrixaban 60 and 80 mg were associated with comparable or slightly less bleeding than warfarin, with a distribution of 1 (0.8%), 5 (3.9%), 5 (3.9%) and 7 (5.5%) patients experiencing a major and/or clinically relevant non-major bleeding respectively.

The composite of stroke, death, and/or systemic non-CNS thromboembolic events occurred in a total of 4 patients, one in each treatment arm (0.8%): 1 ischemic stroke in the 60mg and 80mg groups, and 1 death in the 40 mg and warfarin groups.

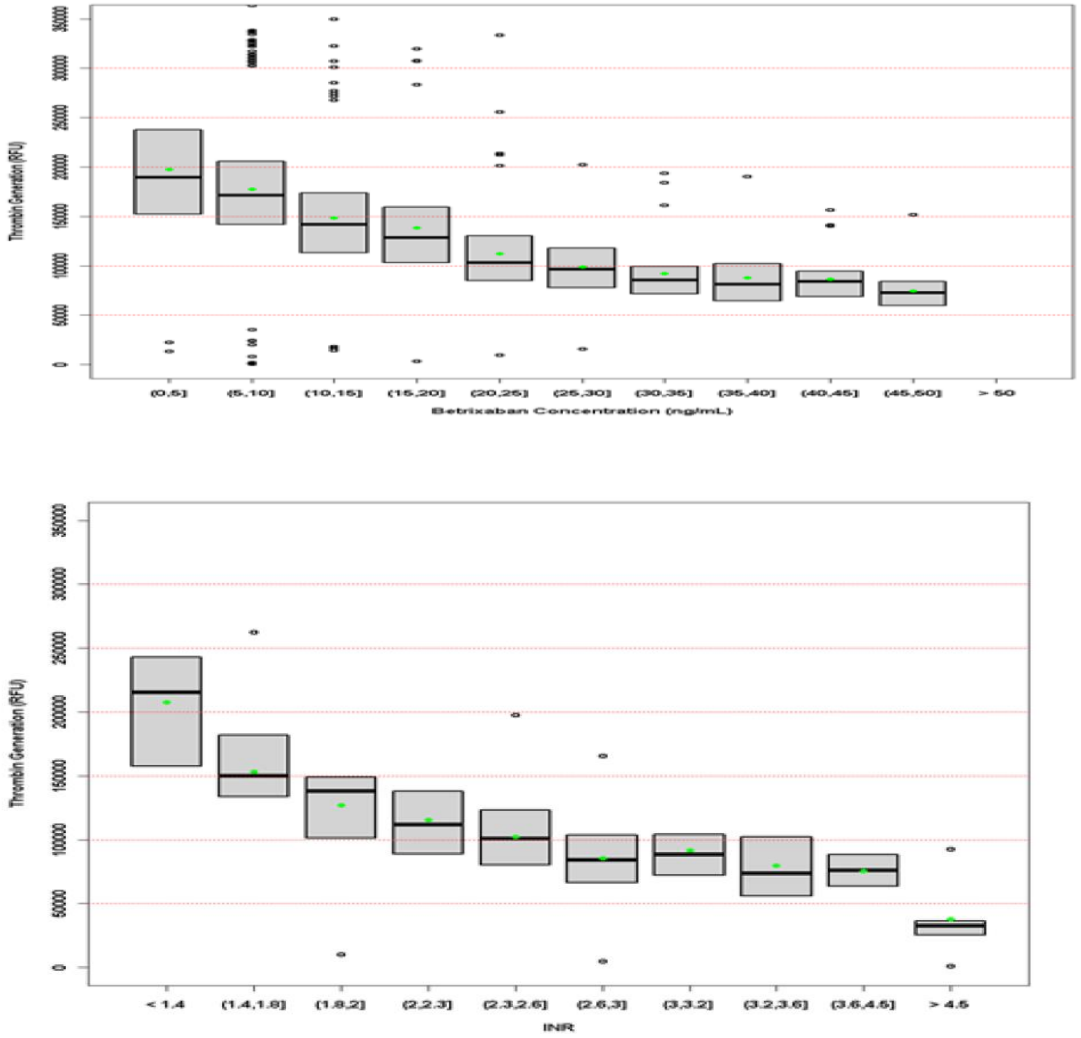
Anti-fXa activity increased with increasing betrixaban dose. Thrombin generation (TG) exhibited a dose-response in betrixaban-treated patients, with lowest levels in the 80 mg group and highest in the 40 mg group. Warfarin resulted in the lowest values.

The Applicant used various models based on the gathering data from EXPLORE Xa, EXPERT, DEC, NC-16-0745 and phase I studies to extrapolate and predict which dose could be the most appropriate in the target population of the pivotal Phase 3 APEX study.

EXPLORE-Xa (POR-PK-BETR-232-002)

The analysis used to select the target betrixaban exposure level for optimal anticoagulation was based in large part on the data obtained in the Phase 2 study, EXPLORE-Xa (Study 08-015) [1]. In this study, assessments of the PK and PD of betrixaban at the doses of 40, 60, and 80 mg were pre-specified as secondary endpoints. The comparator arm consisted of patients taking warfarin adjusted to an INR of 2 to 3. The PD comparison (**Figure 6**) demonstrated that betrixaban at concentrations between 12 and 30 ng/mL caused decreases in TG levels similar to those achieved by warfarin at an INR between 2.0 and 3.0, demonstrating that appropriate therapeutic exposure was obtained at doses used in the EXPLORE-Xa study.

Figure 4. Thrombin Generation Inhibition Achieved with Betrixaban (ng/mL) vs. Warfarin (INR) in EXPLORE -Xa (Study 08-015)



PK-PD Analysis for EXPERT

Steady-state betrixaban concentrations were achieved by the day of discharge (average 4.6 days) with mean observed plasma concentrations of 6.6 ng/mL for betrixaban 15 mg BID and 21.3 ng/mL for betrixaban 40 mg BID. Anticoagulant activity was demonstrated by the inhibition of TG and the level of anti-fXa activity, both of which were affected in a dose- and concentration-dependent manner. The inhibition of TG with betrixaban 15 mg BID (29%) was similar to that observed with enoxaparin while the level of TG inhibition was greater with betrixaban 40 mg BID (35%). In the case of anti-fXa activity, betrixaban at 40 mg BID was equivalent to enoxaparin while the 15 mg betrixaban BID dose was less effective.

2.5.2. Main study

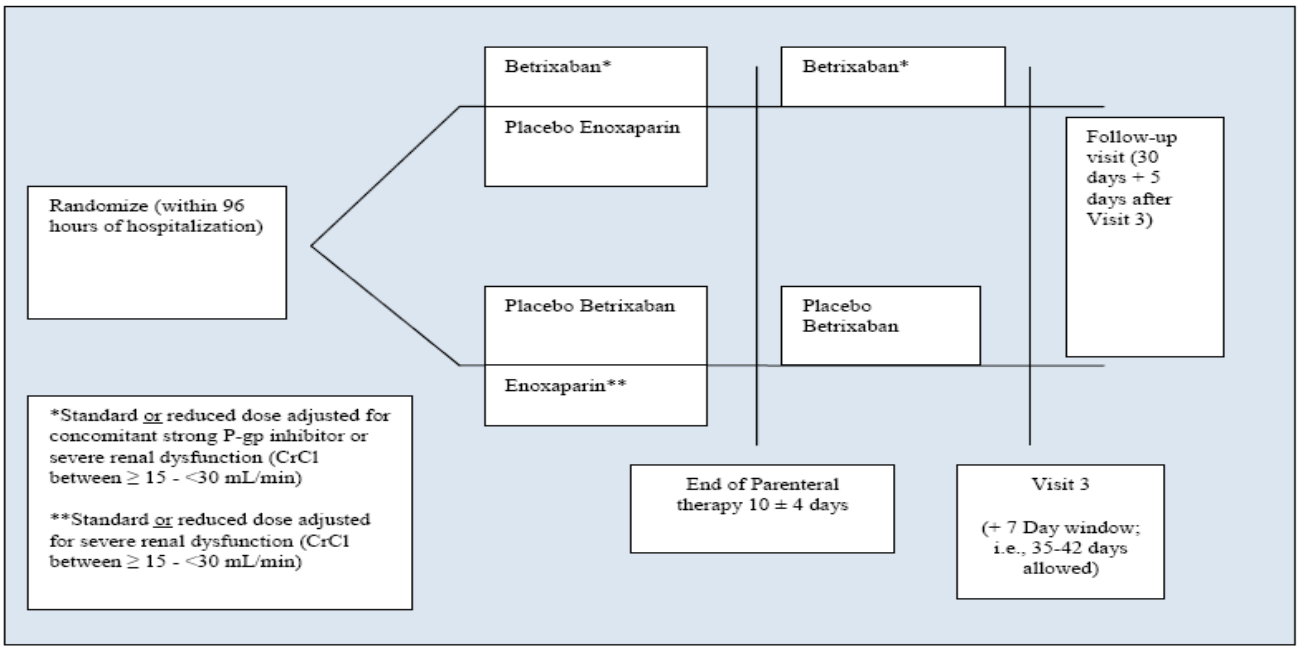
APEX Study: A multi-centre, randomized, active-controlled efficacy and safety study comparing extended duration betrixaban with standard of care enoxaparin for the prevention of venous thromboembolism in acute medically ill patients.

Methods

This was a randomized, double-blind, double-dummy, parallel-group, multicenter, multinational active control superiority study of 35 days (+ 7 day window, i.e., 35 to 42 days allowed) of betrixaban (the test drug) vs. short-term (10 ± 4 days) treatment with parenteral enoxaparin (the active control) for the prevention of VTE events in patients who are at risk due to acute medical illness.

The design of the APEX study is shown in **Figure 7**.

Figure 5. APEX study design schematic



Study Participants

Main Inclusion Criteria (final)

1. General - Male or female patients aged ≥ 40 years.

2. Cause of Acute Hospitalization - At least one of the following as the cause of acute hospitalization:

   a. Acutely decompensated heart failure with prior symptomatic chronic heart failure.

   b. Acute respiratory failure in patients with chronic symptomatic lung disease.

   c. Acute infection without septic shock (e.g., with systolic blood pressure < 90 mmHg after fluid challenge that requires pressor therapy), at screening, and randomization.

   d. Acute rheumatic disorders including acute lumbar pain, sciatica, vertebral compression, rheumatoid arthritis, systemic lupus erythematosus, etc.

   e. Acute ischemic stroke with lower extremity hemiparesis or hemiparalysis, or with immobility of other origin that satisfies protocol immobility requirements.

3. Eligibility Risk Factors - Any one of the following:

a. ≥ 75 years of age, or

b. 60 through 74 years of age with D-dimer ≥ 2 x ULN, or

c. 40 through 59 years of age with D-dimer ≥ 2 x ULN and a history of either VTE (DVT or PE) or cancer (excluding non-melanoma carcinoma of the skin).

4. Immobilization

a. Patients were severely immobilized for 24 hours or were anticipated to be severely immobilized for 24 hours. Severely immobilized meant patients were confined to a bed or chair for the majority of the day and could only be independently mobile to use the in-room toilet. In-bed/chair physical therapy was permitted.

b. After 24 hours of severe immobilization, patients were anticipated to be severely immobilized or moderately immobilized for 3 or more days. Moderately immobilized meant patients could be independently mobile to the in-room or ward toilet; could be mobilized by physical therapy or nursing staff; and could be off-ward with assistance.

6. Length of Hospitalization

a. Expected total length of current hospitalization ≥ 3 days.

b. Enrollment occurred < 96 hours after hospitalization/presentation (e.g., in Emergency Department) for acute medical illness.

Main Exclusion Criteria

General:

1. Unable to receive nourishment by enteral administration (e.g., by mouth, feeding tube, Percutaneous Endoscopic Gastrostomy [PEG] tube).

2. Anticipated need for prolonged anticoagulation during the study.

3. Life expectancy < 8 weeks.

At risk of increased bleeding due to:

6. Low body weight < 45 kg.

7. History of clinically significant bleeding (i.e., requiring medical attention) within 6 months prior to enrollment.

8. History of any significant gastrointestinal, pulmonary, or urogenital bleeding; ongoing chronic peptic ulcer disease; or ongoing or acute gastritis within 2 years prior to enrolment.

9. Admitting or concomitant diagnosis having resulted in or likely to require major surgery (e.g., one in which a body cavity is surgically entered) within 3 months prior to enrolment or while on study, or other invasive procedure performed within 3 months prior to enrolment or while on study.

10. Ophthalmic surgery or biopsy of a parenchymal organ within 3 months prior to enrolment.

11. Contraindication to anticoagulant therapy: a. acquired or inherited bleeding diathesis or coagulopathy, b. bacterial endocarditis, c. uncontrolled arterial hypertension at two consecutive readings, d. platelet count < 100,000 mm3, or activated partial thromboplastin time (aPTT) > 1.4 x ULN or International Normalized Ratio (INR) > 1.4, or requirement for thrombolytic therapy, contraindication to low molecular weight heparins (LMWH).

12. Concomitant drugs/procedures: dual anti-platelet therapy daily, greater than 96 hours of administration of the following anticoagulants immediately prior to receiving study treatment: a. Enoxaparin or another LMWH, b. fondaparinux or c. injections /infusions of unfractionated heparin, oral anticoagulant within 96 hours immediately prior to the beginning of study treatment, indication for fibrinolysis or thrombolysis or having received such therapy within 30 days prior to enrolment, bevacizumab or similar antiangiogenic therapy within 6 months prior to enrolment or planned use during the study period, experimental drugs or devices within 30 days prior to screening.

13. Known history of bronchiectasis (as defined by dilation of the bronchi and associated with bloody sputum in patients with chronic pulmonary disease) or active lung cancer. (However, lung cancer patients post-treatment who have no evidence of residual disease might have been enrolled).

14. End stage renal disease with CrCl < 15 mL/min, or requiring dialysis, or likely to require dialysis within 3 months of enrolment.

15. History of: (a). Spontaneous intracranial (IC) bleeding within 3 years prior to enrolment, or (b). Concurrent IC bleeding including haemorrhagic stroke (or clinical presentation consistent with IC bleeding, if computerized tomography (CT)/magnetic resonance imaging [MRI] not available).

16. History of severe head trauma or other severe physical trauma within 3 months prior to enrolment.

17. Known intracranial lesions, including neoplasm, metastatic disease, arterio-venous malformation, or aneurysm.

Treatments

Betrixaban (experimental) treatment:

Patients received a loading dose of betrixaban (160 mg) on day 1, followed by a daily dose regimen of 80 mg qd, taken with food. The dosage regimen was to be reduced to half (loading dose of 80mg and daily dose of 40 mg) for subjects with one or more of the following factors:

- Severe renal insufficiency (calculated CrCL≤ 30 mL/min),
- Concomitant strong P-gp inhibitors

Patients who developed severe renal impairment or requiring a treatment by strong P-gp inhibitors after randomisation:

- could receive reduced doses of study medication i.e., a 40 mg QD dose of betrixaban (or betrixaban placebo). If renal function improved, patients could either continue the adjusted dose or return to their original assigned doses.
- could have both study drugs interrupted and receive open label enoxaparin for as long as it was required. If renal function improved, patients were allowed to re-start study drugs for up to seven days after interruption.

Patients who developed severe renal dysfunction (i.e., CrCl < 30 mL/min) and required a strong P-gp inhibitor had both study drugs interrupted and received open label enoxaparin for as long as it was required. If the P-gp inhibitor was discontinued or renal function improved, the guidelines above were followed for the patient at the Investigator's discretion.

Enoxaparin (control) treatment

Patient received enoxaparin 4000 UI (40 mg) qd injected subcutaneously. The dosage regimen was to be reduced to half (loading dose of 80mg and daily dose of 40 mg) for subjects with severe renal insufficiency (calculated CrCL≤30 mL/min).

Patients who developed severe renal impairment after randomisation could receive reduced doses of study medication i.e., a 2000 UI (20 mg) QD dose of enoxaparin (or enoxaparin placebo). If renal function improved, patients could either continue the adjusted dose or return to their original assigned doses.

Objectives

The main objective was to demonstrate, in defined study cohorts, the superiority of extended duration (35 days + 7 day window, i.e., 35 to 42 days allowed) anticoagulation with betrixaban as compared to the standard of care (10 ± 4 days) with enoxaparin for prevention of VTE in patients who are at prolonged risk due to acute medical illness and additional risk factors.

Outcomes/endpoints

The primary (composite) outcome was the occurrence of any of the following events through Visit 3 (=35 days ± 7 days):

- Asymptomatic proximal DVT (as detected by ultrasound),
- Symptomatic DVT (proximal or distal),
- Non-fatal PE, or
- VTE-related death.

For the primary efficacy outcome, events were only included if they occurred within a pre-specified day range window described below:

- CUS results will be used if the ultrasound shows an asymptomatic event and it occurred any time after randomization and on or before Day 47.
- CUS results will be used if the ultrasound showed no event and it occurred during the window from Day 32 to 47.

- Symptomatic events were included if they occurred or had onset after randomization and on or before the date of Visit 3. If a patient did not have a Visit 3, events were included only if they had onset after randomization and occurred on or before Day 42 (where the day of randomization was Day 1).

Secondary Efficacy Outcomes

The following were secondary composite outcomes:

- Symptomatic VTE.
- Symptomatic DVTs, non-fatal PEs, and VTE-related deaths with onset on or before Day 42 or the date of Visit 3, if Visit 3 occurred before Day 42.
- The occurrence of asymptomatic proximal DVT (as detected by ultrasound) that occurred on or before Day 47, symptomatic DVT (proximal or distal), non-fatal PE, or all-cause mortality that occurred on or before Day 42 or the date of Visit 3, if Visit 3 occurred before Day 42.

Individual components of the primary efficacy outcome were also considered secondary outcomes:

- The occurrence of asymptomatic proximal DVT (as detected by ultrasound) on or before Day 47. Data will be used as follows:

  – CUS results will be used if the ultrasound shows an asymptomatic event and it occurred any time after randomization and on or before Day 47.

  – CUS results will be used if the ultrasound showed no event and it occurred during the window from Day 32 to 47.

- The occurrence of symptomatic DVT (proximal or distal) that on or before Day 42 or the date of Visit 3, if Visit 3 occurred before Day 42.
- The occurrence of non-fatal PE on or before Day 42 or the date of Visit 3, if Visit 3 occurred before Day 42.
- The occurrence of VTE-related death on or before Day 42 or the date of Visit 3, if Visit 3 occurred before Day 42.

Patients who had multiple events were counted once for each event (at most once for asymptomatic DVT, once for symptomatic DVT, once for non-fatal PE, and once for VTE related death) but may contribute to multiple categories. However, if an asymptomatic event was detected on the same day as, or within two days after the onset of a symptomatic DVT, only the symptomatic DVT was counted as an event.

Primary safety outcome:

The primary safety outcome was the occurrence of major bleeding through seven days after discontinuation of all study medication defined according to the ISTH criteria.

Sample size

The sample size was initially calculated on the event rate of MAGELLAN study, the event rate in the higher risk subgroup was estimated at 9.3% at 35 days. In the APEX study, the enrolled population is similar to the higher risk population in MAGELLAN. Thus, 7.5% was felt to be a conservative estimate of the control group event rate at 35 days in the present study for the overall population.

- Power and level of significance: 90% power for the primary outcome at the 1-sided $\alpha = 0.005$ level in the overall population.

- Expected risk reduction: 35%

With a control group event rate of 7.5%, an assumed relative reduction of 35% at Visit 3, and a single non-binding futility analysis after 50% of the overall population have evaluable primary outcome data, a sample size of 2,568 patients per treatment group with evaluable primary outcome data was computed to provide 90% power for concluding superiority at the 1-sided α = 0.005 level. This same sample size provided 97.1% power for concluding superiority at the 1-sided α = 0.025 level. Assuming that 25% of patients would not be evaluable for the primary outcome, 3,425 patients per treatment group (6,850 patients total) would be required.

As a result of amending the study to test the primary hypothesis first in Cohort 1 (see below: Numbers analysed), which was expected to have a higher event rate than the overall population, the sample size of the study was reassessed. This reassessment was performed when approximately 80% of the evaluable patients had been enrolled.

Event rate: the observed pooled event rates for the primary endpoint were used to re-estimate the sample size based on Cohort 1 only. In order to maintain the number of patient to treat, the power of the study was decreased to 85%, with an estimated relative risk reduction of 35%.

Randomisation

All patients who entered into the Screening Period for the study received a unique patient identification number via the IVRS/IWRS before any study procedures were performed. This number was used to identify the patient throughout the study.

Patients who met the entry criteria were randomized 1:1 to one of the two treatment groups using the IVRS/IWRS at Day 1. This could occur on the same day as Screening.

The randomization was generated using random permuted blocks within geographic region stratified by both dosing criteria and entry criteria, where dosing criteria was defined as whether the patient:

- Had neither severe renal insufficiency nor need for a concomitant strong P-gp inhibitor (resulting in randomization to betrixaban 80 mg [and enoxaparin placebo] or enoxaparin 40 mg [and betrixaban placebo]),
- Had severe renal insufficiency (resulting in randomization to betrixaban 40 mg [and enoxaparin placebo] or enoxaparin 20 mg [and betrixaban placebo]), or
- Was receiving a concomitant strong P-gp inhibitor without severe renal insufficiency (resulting in randomization to betrixaban 40 mg [and enoxaparin placebo] or enoxaparin 40 mg [and betrixaban placebo]).

And where entry criterion was defined as:

- Patient had screening D-dimer ≥ 2 x ULN or < 2 x ULN within 4 days prior to randomization.

Blinding (masking)

The study used a randomized, double-blind, double-dummy design.

Statistical methods

The Primary Efficacy Outcome Population (PEOP) was used for assessing the primary efficacy outcome and included all patients in the mITT population who had assessment of all components of the primary

efficacy outcome endpoint which were necessary to determine (via the adjudication process) whether or not a primary efficacy outcome event had occurred. For detailed descriptions of the analysis populations, see below under "Numbers analysed".

Betrixaban was compared to enoxaparin through a closed testing, gate-keeping procedure that sequentially tested the primary and secondary efficacy composite outcome hypothesis in each of the cohorts in seven steps (**Figure 8**).

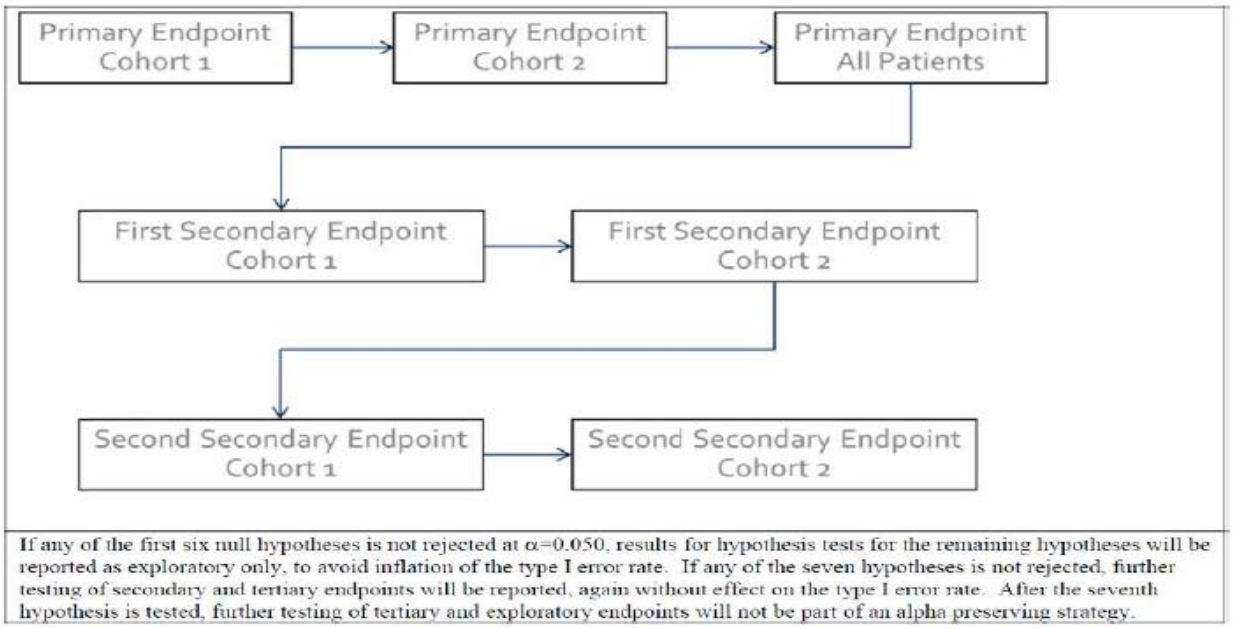
The initial test (Step 1) compared betrixaban and enoxaparin with respect to the primary efficacy endpoint in the primary patient population (Cohort 1) using the Mantel-Haenszel test stratified by dosing criteria. If the comparison achieved statistical significance at the 2-sided 0.05 level, then the second test (Step 2) compared the primary efficacy endpoint between the two treatment groups in Cohort 2 based on the Mantel-Haenszel test stratified by dosing and entry criteria. The dosing and entry criteria were defined by data from local laboratory measurements, and patients without local laboratory measurements were considered to not have severe renal insufficiency; patients without a strong P–gp inhibitor in concomitant meds were considered not to be receiving one.

In the third step the Primary Efficacy Composite Outcome was tested in the entire PEOP. If all of those tests were significant the First Secondary Efficacy Outcome was tested in Cohort 1 followed by Cohort 2 and then the Second Secondary Efficacy Outcome was tested in Cohort 1 followed by Cohort 2.

If at any step the null hypothesis was not rejected at the 2-sided 0.05 significance level, then the rest of the hypothesis testing was considered exploratory.

As the study-wise error was maintained with the above procedure, there was no α penalty associated with it.

Figure 6. Graphical Depiction of the Multiple Testing Procedure



Interim analysis

One non-binding futility analysis was planned for the IDMC when approximately 50% (i.e., approximately 2,568 evaluable patients) of the overall population had evaluable primary outcome data. In addition, interim safety analyses were performed after 250, 750, 1,500, 3,000, and 4,500 patients had completed Visit 3.

Sensitivity analysis and Handling of Missing Data

With regard to the primary and second secondary efficacy outcomes, a sensitivity analysis was performed by imputing the missing CUS values for the asymptomatic component of the composite endpoints.

A method described by Quan et al for the analysis of a binary composite outcome with missing data in components was used. For this analysis, the four components of the primary efficacy analysis (asymptomatic proximal DVT, symptomatic DVT, non-fatal PE or VTE-related death) were collapsed into a two component composite outcome (asymptomatic proximal DVT, or symptomatic event). Further, it was assumed that symptomatic events would be fully observed, so only one component of the composite will have missing data. All patients in the mITT analysis set were used in this sensitivity analysis, even those patients not in the primary efficacy outcome evaluable population. Patients who were in the mITT set but not in the PEOP were those considered missing the asymptomatic component of the primary efficacy endpoint, subject to the method of Quan et al.

In addition to the sensitivity analyses using Quan's method, other sensitivity analyses were conducted to examine the nature of missingness for patients without evaluable primary efficacy data in Cohort 1 and in Cohort 2 of the PEOP.

Results

Participant flow

Overall there were 8,589 patients screened and 7,513 randomized into the study. Of all randomized patients, 72 patients (38 on Betrixaban and 34 on Enoxaparin) were excluded from the PEOP and because they did not receive any dose of study drug and another 1,155 patients (609 on Betrixaban and 546 on Enoxaparin) excluded from the PEOP because they did not have a symptomatic event associated with venous thromboembolism and did not have evaluable CUS results available between Day 32 and Day 47. There were 7,441 patients in mITT Population and 6,286 patients in PEOP.

Recruitment

Study start date: 29 March 2012 (First patient enrolled)

Study completion date: 15 January 2016 (Last patient completed)

Conduct of the study

Significant protocol deviations in the randomised population are summarised in **Table 25**.

Table 20. Significant Protocol Deviations – Randomized Population (APEX Study)

Deviation Type	Betrixaban (N=3,759) n (%)	Enoxaparin (N=3,754) n (%)	Total (N=7,513) n (%)
Overall	833 (22.2)	742 (19.8)	1,575 (21.0)
Do not meet important inclusion/exclusion criteria	134 (3.6)	127 (3.4)	261 (3.5)
Incorrect drug dispensed and administered	7 (0.2)	6 (0.2)	13 (0.2)
Have substantial use of any disallowed medication	226 (6.0)	197 (5.2)	423 (5.6)
Have study medication compliance < 80% for the treatment assigned	66 (1.8)	65 (1.7)	131 (1.7)
Have early (before day 32) or late (after day 47) visit 3 or CUS, inadequate CUS, or missed CUS or other efficacy assessment, in the absence of an adjudicated symptomatic event	514 (13.7)	450 (12.0)	964 (12.8)
Other	3 (< 0.1)	6 (0.2)	9 (0.1)

Note: Percentages are based on the total number of the randomized patients in each treatment group. Patients could have more than one significant protocol deviation.

There were four amendment to the original protocol dated 13 February 2012. The first two amendments revised some of the inclusion, exclusion and immobility criteria.

Amendment 3, dated 04 June 2014, made the following major changes:

- Enrichment of the study patient population to maximize clinical benefit and optimize patient selection for treatment, including those with baseline D-dimer ≥ 2x ULN and/or age ≥ 75 years (union). Further enrolment of patients in the biomarker negative subgroup (age <75 and D-dimer <2x ULN) will cease;
- A modification to the primary analysis, testing study cohorts of patients sequentially in the order of anticipated risk of VTE. Patient populations to be analysed for efficacy include (a) Cohort 1: Primary Patient Population: Patients who have Ddimer ≥ 2x ULN at baseline (b) Cohort 2: Patients who have D-dimer ≥ 2x ULN and/or age ≥ 75 years (union);
- Introduction of a single planned sample size re-assessment when approximately 80% of evaluable patients have been enrolled;

Changes were also made to the hierarchy of some exploratory endpoints. Additional safety outcomes were added together with a requirement for compression ultrasound in all patients at Visit 3. Some further changes were introduced in relation to D-dimer testing and a modification to Outcome Adjudication and Definitions to specify that Sudden deaths without assignable cause would no longer be considered VTE related.

Amendment 4, dated 28 January 2016, clarified the populations and the day range windows of events and for compression ultrasound to be used for the analysis of the primary and secondary endpoints.

Baseline data

Demographics and other baseline characteristics are found in **Table 26**.

Table 21. Demographics and Baseline Characteristics – Randomized Population (APEX Study)

	Betrixaban (N=3,759)	Enoxaparin (N=3,754)	Total (N=7,513)
Age (years)			
N	3,759	3,754	7,513
Mean (SD)	76.6 (8.46)	76.2 (8.31)	76.4 (8.39)
Median	77.0	77.0	77.0
Q1, Q3	72.0, 82.0	72.0, 82.0	72.0, 82.0
Min, Max	40, 103	40, 102	40, 103
Age Category N (%)			
< 75 Years	1,184 (31.5)	1,237 (33.0)	2,421 (32.2)
≥ 75 Years	2,575 (68.5)	2,517 (67.0)	5,092 (67.8)
Gender N (%)			
Male	1,705 (45.4)	1,720 (45.8)	3,425 (45.6)
Female	2,054 (54.6)	2,034 (54.2)	4,088 (54.4)
Race N (%)			
White	3,503 (93.2)	3,518 (93.7)	7,021 (93.5)
Black or African American	74 (2.0)	73 (1.9)	147 (2.0)
Asian	9 (0.2)	7 (0.2)	16 (0.2)
American Indian or Alaska Native	4 (0.1)	4 (0.1)	8 (0.1)
Native Hawaiian or Other Pacific Islander	0	1 (< 0.1)	1 (< 0.1)
Multiple	26 (0.7)	26 (0.7)	52 (0.7)
Other	62 (1.6)	55 (1.5)	117 (1.6)
Data Collection Prohibited by Regulation	81 (2.2)	70 (1.9)	151 (2.0)
Ethnicity N (%)			
Hispanic or Latino	405 (10.8)	426 (11.3)	831 (11.1)
Not Hispanic or Latino	3,260 (86.7)	3,246 (86.5)	6,506 (86.6)
Data Collection Prohibited by Regulation	94 (2.5)	82 (2.2)	176 (2.3)
Height at Screening (cm)			
N	3,724	3,716	7,440
Mean (SD)	165.37 (9.138)	165.35 (9.117)	165.36 (9.127)
Median	165.00	165.00	165.00
Q1, Q3	160.00, 172.00	160.00, 172.00	160.00, 172.00
Min, Max	120.0, 201.0	137.0, 200.7	120.0, 201.0

	Betrixaban (N=3,759)	Enoxaparin (N=3,754)	Total (N=7,513)
Weight at Screening (kg)			
N	3,752	3,747	7,499
Mean (SD)	79.84 (19.210)	80.74 (19.347)	80.29 (19.282)
Median	78.00	78.00	78.00
Q1, Q3	66.00, 90.00	68.00, 91.00	67.00, 90.20
Min, Max	40.0, 200.0	35.6, 188.4	35.6, 200.0
Body Mass Index (BMI) at Screening (kg/m²)			
N	3,724	3,716	7,440
Mean (SD)	29.21 (6.596)	29.54 (6.674)	29.37 (6.637)
Median	28.10	28.40	28.30
Q1, Q3	24.70, 32.90	24.80, 33.30	24.80, 33.10
Min, Max	15.2, 85.3	14.7, 77.3	14.7, 85.3
Anticoagulant Use Prior to Randomization N (%)			
Yes	1,928 (51.3)	1,879 (50.1)	3,807 (50.7)
No	1,831 (48.7)	1,874 (49.9)	3,705 (49.3)
Missing	0	1 (< 0.1)	1 (< 0.1)
Mobility Assessment at Screening N (%)			
Severe Immobilization	3,656 (97.3)	3,652 (97.3)	7,308 (97.3)
Moderate Immobilization	95 (2.5)	96 (2.6)	191 (2.5)
Neither Moderate nor Severe Immobilization	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)
Missing	7 (0.2)	5 (0.1)	12 (0.2)
Dosing Criteria N (%)			
Has Severe Renal Insufficiency	175 (4.7)	150 (4.0)	325 (4.3)
Is Receiving a Concomitant Strong P-Gp Inhibitor Without Severe Renal Insufficiency	677 (18.0)	649 (17.3)	1,326 (17.6)
Has Neither Severe Renal Insufficiency nor Need for a Concomitant Strong P-Gp Inhibitor	2,907 (77.3)	2,955 (78.7)	5,862 (78.0)
Entry Criteria N (%)			
D-dimer ≥ 2 x ULN	2,341 (62.3)	2,332 (62.1)	4,673 (62.2)
D-dimer < 2 x ULN	1,382 (36.8)	1,386 (36.9)	2,768 (36.8)
Missing	36 (1.0)	36 (1.0)	72 (1.0)
Duration of Hospitalization at Entry (days)			
N	3,684	3,697	7,381
Mean (SD)	11.3 (6.35)	11.6 (6.79)	11.4 (6.57)
Median	10.0	10.0	10.0
Q1, Q3	7.0, 14.0	8.0, 14.0	8.0, 14.0
Min, Max	1, 85	1, 90	1, 90
IMPROVE Score			
N	3,759	3,754	7,513
Mean (SD)	1.5 (1.06)	1.5 (1.04)	1.5 (1.05)
Median	1.0	1.0	1.0
Q1, Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0
Min, Max	0, 8	0, 7	0, 8
IMPROVE Score Category N (%)			
Lower Risk (IMPROVE Score < 2)	2,760 (73.4)	2,800 (74.6)	5,560 (74.0)
Higher Risk (IMPROVE Score ≥ 2)	999 (26.6)	954 (25.4)	1,953 (26.0)

Note: Percentages are based on the total number of the randomized patients in each treatment group. D-dimer values were determined by the local lab.

To be eligible for enrolment, patients were required to present with at least one of the primary causes of acute hospitalization / primary risk criteria (i.e., acutely decompensated heart failure, acute respiratory failure, acute infection, acute rheumatic disorders, or acute ischemic stroke).

A summary of the number and percent of patients in the Randomized Population with each primary risk criterion as well as other risk factors is provided in **Table 27**.

Table 22. Cause of Acute Hospitalization / Primary Risk Criteria and Other Risk Factors – Randomized Population

	Betrixaban (N=3,759) **n** (%)	**Enoxaparin** (N=3,754) **n** (%)	**Total** (N=7,513) **n** (%)
Primary Risk Criteria for VTE Documented as the Cause of the Acute Hospitalization *			
Acutely Decompensated Heart Failure	1,677 (44.6)	1,672 (44.5)	3,349 (44.6)
Acute Respiratory Failure	448 (11.9)	474 (12.6)	922 (12.3)
Acute Infection Without Septic Shock	1,112 (29.6)	1,058 (28.2)	2,170 (28.9)
Acute Rheumatic Disorders	109 (2.9)	117 (3.1)	226 (3.0)
Acute Ischemic Stroke	411 (10.9)	432 (11.5)	843 (11.2)
Risk Factors			
Previous History of VTE (DVT Or PE) or Superficial Venous Thrombosis	312 (8.3)	296 (7.9)	608 (8.1)
Obesity (BMI > 35)	679 (18.1)	734 (19.6)	1413 (18.8)
Previous Documented Chronic Venous Insufficiency or Severe Varicosis of the Lower Extremity	702 (18.7)	690 (18.4)	1392 (18.5)
Lower Extremity Paresis or Hemiparesis or Hemiparalysis	294 (7.8)	277 (7.4)	571 (7.6)
Hormone Therapy (antiandrogen, estrogen, progesterone or Selective Estrogen Receptor Modulators [SERMS])	43 (1.1)	31 (0.8)	74 (1.0)
History of Cancer Excluding Non-Melanoma Carcinoma of the Skin	466 (12.4)	443 (11.8)	909 (12.1)
Chronic Heart Failure (NYHA Class III or IV)	853 (22.7)	865 (23.0)	1,718 (22.9)
Chronic Respiratory Failure	933 (24.8)	893 (23.8)	1,826 (24.3)
Active Collagen Vascular Disease Associated with Limited Mobility (e.g., isolated Sicca Syndrome will not qualify)	93 (2.5)	93 (2.5)	186 (2.5)
Acute Infectious Disease Contributing to Current Hospitalization	602 (16.0)	620 (16.5)	1,222 (16.3)
Current Concomitant Use of Erythropoeisis Stimulating Agents	4 (0.1)	3 (< 0.1)	7 (< 0.1)
Inherited or Acquired Thrombophilia	3 (< 0.1)	5 (0.1)	8 (0.1)
Number of Risk Factors			
0	1,007 (26.8)	993 (26.5)	2,000 (26.6)
1	1,225 (32.6)	1,258 (33.5)	2,483 (33.0)
2	992 (26.4)	962 (25.6)	1,954 (26.0)
3	391 (10.4)	411 (10.9)	802 (10.7)
4	120 (3.2)	111 (3.0)	231 (3.1)
> 4	24 (0.6)	18 (0.5)	42 (0.6)

Note: Percentages are based on the total number of the randomized patients in each treatment group. Two patients in the betrixaban group and one patient in the enoxaparin group did not have a primary risk factor. The patient in the enoxaparin arm had a stroke on admission which was not confirmed; the patient was randomized but not dosed. The two patients in the betrixaban group were admitted with stroke: stroke was not confirmed post admission.

Numbers analysed

The following populations within the study were defined:

Primary Efficacy Outcome Population (PEOP)

The PEOP was used for assessing the primary efficacy outcome, and included all patients in the mITT population who had assessment of all components of the primary efficacy outcome endpoint which were necessary to determine (via the adjudication process) whether or not a primary efficacy outcome

event had occurred. Because no data were imputed for the primary analysis of the primary endpoint, the PEOP was the subset of patients in the mITT who had data available for analysis. Specifically, for the primary analysis of the primary endpoint, the patients in this population were those included in the mITT population who had one or more of the following:

- Evaluable CUS results if the ultrasound showed an asymptomatic event and it occurred any time after randomization and on or before Day 47;
- An evaluable CUS result if the ultrasound showed no event and it occurred during the window from Day 32 to 47;
- An adjudicated symptomatic DVT/PE after randomization and on or before Day 42 or the date of Visit 3, if Visit 3 occurred before Day 42;
- An adjudicated VTE-related death, defined as a death adjudicated as a confirmed, probable, or possible fatal PE/VTE after randomization on or before Day 42 or the date of Visit 3, if Visit 3 occurred before Day 42;
- For the third and fourth bullets, only events adjudicated by the CEC as meeting the definition of the primary efficacy endpoint were to count for inclusion. Events considered by the CEC but rejected as not meeting the criteria would not count and patients with such events would not be in the primary efficacy outcome population unless they had another event that was adjudicated as meeting the definition of a primary efficacy endpoint, or an evaluable ultrasound, as described above. In the transfer of data from the CEC, endpoints that result in inclusion would have Status = 'Complete' and EventType = 'Symptomatic DVT' or 'Pulmonary Embolism' or ('Death' and DTHCAUS = 'Fatal PE/VTE'). No other results from the CEC were to result in inclusion in the Primary Efficacy Outcome Population.

The PEOP was the analysis set used for the primary efficacy analysis, and in particular was used for the first three steps of the sequential gatekeeper procedure

Modified Intent-to-Treat (mITT)

The mITT population consisted of all patients who had taken at least one dose of study drug and who had follow-up assessment data on one or more primary or secondary efficacy components. It was assumed that all patients who took one dose of study drug would have been assessed for one or more components of efficacy during follow-up, which began immediately at administration of the first dose.

First Secondary Efficacy Outcome Population (FSEOP)

The FSEOP was used for assessing the first secondary efficacy outcome, and included all patients in the mITT population. Patients were counted as having an event if they had one or more of the following:

- An adjudicated symptomatic DVT/PE after randomization and on or before Day 42 or the date of Visit 3, if Visit 3 occurred before Day 42;
- An adjudicated VTE-related death, defined as a death adjudicated as a confirmed, probable, or possible fatal PE/VTE after randomization on or before Day 42 or the date of Visit 3, if Visit 3 occurred before Day 42.

All other patients were counted as not having an event.

Second Secondary Efficacy Outcome Population (SSEOP)

The Second Secondary Efficacy Outcome Population (SSEOP) included all patients in the mITT Population who had assessment of all components of the second secondary efficacy outcome endpoint

which were necessary to determine (via the adjudication process) whether or not a second secondary efficacy outcome event had occurred. Patients were included in the SSEOP if they had a second secondary endpoint or if they had an evaluable CUS result if the ultrasound showed no event and it occurred during the window from Day 32 to 47. Patients were counted as having an event if they had one or more of the following:

- Evaluable CUS results if the ultrasound showed an asymptomatic event and it occurred any time after randomization and on or before Day 47;
- An adjudicated symptomatic DVT/PE after randomization and on or before Day 42 or the date of Visit 3, if Visit 3 occurred before Day 42;
- An adjudicated VTE-related death, defined as any death (whether or not adjudicated as a confirmed, probable, or possible fatal PE/VTE) after randomization on or before Day 42 or the date of Visit 3, if Visit 3 occurred before Day 42;
- An adjudicated non VTE-related death after randomization on or before Day 42 or the date of Visit 3, if Visit 3 occurred before Day 42.

All other patients would be counted as not having an event.

Per Protocol Population (PP)

All patients who were in the mITT analysis population, with no significant protocol deviations, and with sufficient compliance for each treatment were included. For enoxaparin administration, the patient must have received at least 80% of the minimum planned dosing, unless an event occurred before this could be accomplished. For betrixaban administration, a patient must have received at least 80% of the number of planned capsules.

Cohorts

Cohort 1 and Cohort 2 were defined within each analysis population.

- Cohort 1 of the population consisted of all members of the population/subset with D-dimer value at baseline of at least 2 x ULN (as measured by the local lab).
- Cohort 2 of the population consisted of all members of the population with D-dimer value at baseline of at least 2 x ULN (as measured by the local lab), or age at least 75 years of age. D-dimer values at screening were also assessed by the central laboratory.

Outcomes and estimation

Primary efficacy outcome

A summary of the pre-specified analysis of the primary efficacy outcome is presented in **Table 28**.

Table 23. Summary of Pre-specified Analyses of the Primary Efficacy Outcome

Analysis	Betrixaban Event Rate % (95% CI) [1]	Enoxaparin Event Rate % (95% CI) [1]	Relative Risk Reduction (95% CI) [2]	Unadjusted p-Value [3]
Step 1: Analysis of the Primary Efficacy Endpoint – PEOP – Cohort 1	6.90 (5.76, 8.03)	8.49 (7.25, 9.72)	0.194 (-0.004, 0.353)	0.054
Step 2: Analysis of the Primary Efficacy Endpoint – PEOP – Cohort 2	5.63 (4.78, 6.48)	7.05 (6.12, 7.98)	0.200 (0.023, 0.345)	0.029
Step 3: Analysis of the Primary Efficacy Endpoint – PEOP	5.30 (4.51, 6.09)	7.03 (6.14, 7.91)	0.240 (0.077, 0.375)	0.006

First secondary efficacy outcome

Steps 4 and 5 of the closed testing gate-keeping procedure were conducted on the first secondary efficacy outcome (VTE-related death, non-fatal PE and symptomatic DVT) in Cohort 1 and Cohort 2 of the FSEOP (**Table 29**).

Table 24. Summary of Analyses of the First Secondary Efficacy Outcomes

Analysis	Betrixaban Event Rate % (95% CI) [1]	Enoxaparin Event Rate % (95% CI) [1]	Relative Risk Reduction (95% CI) [2]	Unadjusted p-Value [3]
Step 4: Analysis of the First Secondary Efficacy Outcome – FSEOP – Cohort 1	1.30 (0.84, 1.76)	1.90 (1.35, 2.46)	0.326 (-0.069, 0.576)	0.092
Step 5: Analysis of the First Secondary Efficacy Outcome – FSEOP – Cohort 2	1.03 (0.69, 1.37)	1.45 (1.04, 1.85)	0.295 (-0.085, 0.542)	0.110
Analysis of the First Secondary Efficacy Outcome – FSEOP	0.94 (0.63, 1.25)	1.45 (1.07, 1.84)	0.358 (0.020, 0.580)	0.039

Second secondary efficacy outcomes

Steps 5 and 6 of the closed testing gate-keeping procedure were conducted on the second secondary efficacy outcome in Cohort 1 and Cohort 2 of the SSEOP (**Table 30**). Although not part of the testing procedure, the second secondary efficacy outcome was also analysed in the SSEOP, overall.

Table 25. Summary of Analyses of the Second Secondary Efficacy Outcomes

Analysis	Betrixaban Event Rate % (95% CI) [1]	Enoxaparin Event Rate % (95% CI) [1]	Relative Risk Reduction (95% CI) [2]	Unadjusted p-Value [3]
Step 6: Analysis of the Second Secondary Efficacy Outcome – SSEOP – Cohort 1	11.52 (10.13, 12.91)	12.85 (11.41, 14.30)	0.111 (-0.049, 0.246)	0.164
Step 7: Analysis of the Second Secondary Efficacy Outcome – SSEOP – Cohort 2	9.79 (8.72, 10.86)	10.90 (9.79, 12.01)	0.105 (-0.039, 0.229)	0.146
Analysis of the Second Secondary Efficacy Outcome – SSEOP	9.18 (8.19, 10.18)	10.85 (9.79, 11.91)	0.155 (0.022, 0.270)	0.024

Individual components of the primary efficacy outcome

Individual components of the primary efficacy outcome were also considered secondary outcomes and are presented in **Table 31.**

Table 26. Analysis of Primary Efficacy Outcome (Asymptomatic Proximal DVT, Symptomatic DVT, Non-Fatal PE, or VTE-Related Death through Visit 3) – PEOP – Cohort 1 (Local Lab)

	Betrixaban (N=1,914)	Enoxaparin (N=1,956)
Number of Patients with At Least One Event n (%) [1 2]	132 (6.9)	166 (8.5)
At Least One Symptomatic Event [1]	30 (1.6)	44 (2.2)
VTE-Related Death	12 (0.6)	11 (0.6)
At Least One Non-Fatal Pulmonary Embolism	5 (0.3)	17 (0.9)
At Least One Symptomatic DVT	14 (0.7)	19 (1.0)
At Least One Asymptomatic Event	105 (5.5)	129 (6.6)
Number of Patients with No Event n (%) [2]	1,782 (93.1)	1,790 (91.5)
Event Rate % (95% CI) [2]	6.90 (5.76, 8.03)	8.49 (7.25, 9.72)
Relative Risk (95% CI) [2]	0.806 (0.647, 1.004)	
p-Value [3]	0.054	
Relative Risk Reduction [4] (95% CI)	0.194 (-0.004, 0.353)	

Tertiary/exploratory efficacy outcomes

Analysis of the primary endpoint through the end of parenteral therapy is presented in **Table 32** and data on all-cause death through visit 3 in **Table 33**.

Table 27. Analysis of All-Cause Death through Visit 3 – FSEOP

	Betrixaban (N=3,721)	Enoxaparin (N=3,720)
Number of Patients with At Least One Event n (%) [1]	147 (4.0)	154 (4.1)
VTE-Related Death	13 (0.3)	17 (0.5)
Non-VTE Related Death	134 (3.6)	137 (3.7)
Number of Patients with No Event n (%) [1]	3,574 (96.0)	3,566 (95.9)
Event Rate % (95% CI) [1]	3.95 (3.32, 4.58)	4.14 (3.50, 4.78)
Relative Risk (95% CI) [2]	0.947 (0.758, 1.185)	
p-Value [2]	0.635	
Relative Risk Reduction [3] (95% CI)	0.053 (-0.185, 0.242)	

[1] Percentages and event rates are based on the total number of the FSEOP patients in each treatment group.

[2] Relative Risk (betrixaban arm versus enoxaparin arm) represents the ratio of the proportions of the patients who died through Visit 3 or Day 42, whichever is earlier in betrixaban group and enoxaparin group. Both Relative Risk and p-value are based on the Mantel-Haenszel test stratified by the dosing criteria and the entry criteria.

[3] Relative Risk Reduction is calculated as 1–Relative Risk.

Table 28. Analysis of Symptomatic DVT, Non-Fatal PE, or VTE-Related Death through the End of Parenteral Therapy – FSEOP

	Betrixaban (N=3,721)	Enoxaparin (N=3,720)
Number of Patients with At Least One Event n (%)[1 2]	7 (0.2)	9 (0.2)
At Least One Symptomatic Event [1]	7 (0.2)	9 (0.2)
VTE-Related Death	2 (< 0.1)	2 (< 0.1)
At Least One Non-Fatal Pulmonary Embolism	2 (< 0.1)	6 (0.2)
At Least One Symptomatic DVT	3 (< 0.1)	1 (< 0.1)
Number of Patients with No Event n (%) [2]	3,714 (99.8)	3,711 (99.8)
Event Rate % (95% CI) [2]	0.19 (0.05, 0.33)	0.24 (0.08, 0.40)
Relative Risk (95% CI) [3]	0.764 (0.284, 2.050)	
p-Value [3]	0.591	
Relative Risk Reduction [4] (95% CI)	0.236 (-1.050, 0.716)	

[1] A patient may have more than one event. A patient is counted once for each row if the patient reported more than one event. Therefore, numbers may add up to a larger number than total.

[2] Percentages and event rates are based on the total number of the FSEOP patients in each treatment group.

[3] Relative Risk (betrixaban arm versus enoxaparin arm) represents the ratio of the proportions of the patients who have developed at least one of the events in the composite outcome (Symptomatic VTE through the end of parenteral therapy) in betrixaban group and enoxaparin group. Both Relative Risk and p-value are based on the Mantel-Haenszel test stratified by the dosing criteria and the entry criteria.

[4] Relative Risk Reduction is calculated as 1–Relative Risk.

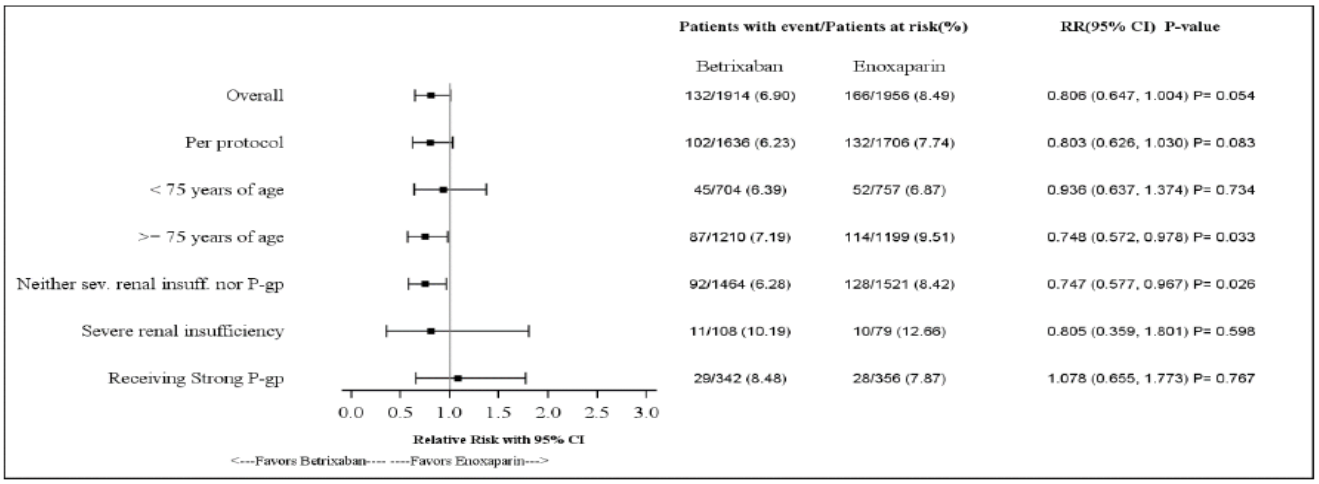
Ancillary analyses

Additional analyses of the primary efficacy outcome, both pre-specified and post hoc, in patients in Cohort 1 were conducted and presented by the applicant:

- An *alternative* analysis, that included an additional patient (Patient X) as having qualified as meeting the primary efficacy endpoint in Cohort 1 (contrary to how this patient was handled in the initial analysis of the primary efficacy endpoint), resulted in a RRR of 19.8% (nominal p = 0.048).
- In the *pre-specified* analysis for which inclusion of patients in Cohort 1 was based solely on central lab D-dimer values instead of local lab D-dimer values, the event rate % (95% CI) in the Betrixaban arm was 6.42 (5.30, 7.54) vs 9.06 (7.74, 10.37) in the Enoxaparin arm.
- In the *pre-specified* analysis for which inclusion of patients in Cohort 1 based on local lab D-dimer values, or central lab D-dimer values if local lab values were not available, the event rate % (95% CI) was 6.84 (5.72, 7.97) in the Betrixaban arm and 8.49 (7.25, 9.72) in the Enoxaparin arm.
- There were *five pre-specified sensitivity analyses* of the primary efficacy outcome in patients in Cohort 1 that varied the windows for including events in the analysis. The event rate % in the Betrixaban arm in these analyses ranged from 6.89-7.26 and the event rate % in the Enoxaparin arm ranged from 8.14-8.94.
- In the *pre-specified* analysis of the primary efficacy outcome by dosing criteria, patients with neither severe renal insufficiency nor need for a strong P-gp inhibitor randomized to 80 mg Betrixaban had an event rate of 6.28% vs. 8.42% in patients receiving Enoxaparin (nominal p = 0.026).
- A *post-hoc sensitivity analysis* of the primary efficacy outcome in Cohort 1 in which only patients that actually received 80 mg or 40 mg Betrixaban or matching placebo were included, the overall event rate % in patients who received the 80 mg dose Betrixaban was 6.27% Betrixaban vs. 8.39% for Enoxaparin (nominal p = 0.023) while the event rate % in patients that received the 40 mg dose were 9.32 in the Betrixaban group and 8.66 in the Enoxaparin group (nominal p=0.800).
- A *pre-specified sensitivity analysis* of the primary efficacy outcome in Cohort 1 of the mITT Population was conducted by imputing the missing CUS values for the asymptomatic component of the composite outcome using Quan's method. The event rate and RRR favoured Betrixaban; RRR 18.6% (p = 0.067).

A selection of the planned sub-group analyses Cohort 1 for the primary efficacy analysis, based on various baseline criteria are presented as Forest plots in **Figure 9**.

Figure 7. Forest Plot of the Subgroup Analyses of the Primary Efficacy Outcome – PEOP – Cohort 1



Two different ways of assessing "Net Clinical Benefit" were included as exploratory outcomes in the APEX study: 35-Day Net Clinical Benefit calculated as the composite of the primary efficacy outcome plus major bleeding on or before Day 42 or the date of Visit 3, if Visit 3 occurred before Day 42 and Net Clinical Benefit through the time of parenteral study medication discontinuation – the composite of the symptomatic VTE outcome (VTE-related death, nonfatal PE, or symptomatic DVT) plus major bleeding from randomization through the last day of parenteral study medication. In response to the CHMP's questions, the applicant also presented the outcome of new, post hoc analysis of Net Clinical Benefit (**Table 34**).

Table 29. Summary of net clinical benefit analyses in the APEX study

Composite Endpoint	Population	Betrixaban n/N (%)	Enoxaparin n/N (%)	Relative Risk	95% CI	p-Value	ARR (%)	NNT
Primary Efficacy Outcome (asymp. & symp. DVT + non-fatal PE + VTE-related death) + Major Bleeding	PEOP - Cohort 1 (Local D-dimer)	141/1,914 (7.4)	174/1,956 (8.9)	0.82	0.66–1.01	0.07	1.5	-
	PEOP- Cohort 1 (Central D-dimer)	126/1,838 (6.9)	171/1,822 (9.4)	0.73	0.58–0.90	0.004	2.5	40
	PEOP - Cohort 2 (Local D-dimer)	174/2,842 (6.1)	214/2,893 (7.4)	0.82	0.68–1.00	0.05	1.3	-
	PEOP- Cohort 2 (Central D-dimer)	167/2,741 (6.1)	207/2,771 (7.5)	0.79	0.65–0.97	0.021	1.4	72
	PEOP - overall (Local D-dimer)	179/3,112 (5.8)	233/3,174 (7.3)	0.78	0.65–0.94	0.009	1.5	67
	PEOP - 80 mg, Cohort 1	100/1,516 (6.6)	135/1,549 (8.7)	0.76	0.59–0.97	0.026	2.1	48
	PEOP - 80 mg, Cohort 2	126/2,276 (5.5)	170/2,330 (7.3)	0.75	0.60–0.94	0.013	1.8	56
	PEOP - 80 mg, overall	131/2,506 (5.2)	188/2,562 (7.3)	0.71	0.57–0.89	0.002	2.1	48
	mITT - overall	192/3,721 (5.2)	246/3,720 (6.6)	0.78	0.65–0.93	0.007	1.4	72
	mITT - overall (80 mg)	137/2,878 (4.8)	195/2,926 (6.7)	0.72	0.58–0.88	0.002	1.9	53

Composite Endpoint	Population	Betrixaban n/N (%)	Enoxaparin n/N (%)	Relative Risk	95% CI	p-Value	ARR (%)	NNT
Fatal or Irreversible Events (Non-haemorrhagic cardiopulmonary death + non-fatal pulmonary embolism + myocardial infarction + ischemic stroke + fatal bleeding + Intracranial haemorrhage)	mITT - Cohort 1	82/2,314 (3.5)	111/2,313 (4.8)	0.73	0.55–0.97	0.028	1.3	77
	mITT - Cohort 2	105/3,407 (3.1)	139/3,391 (4.1)	0.74	0.58–0.95	0.017	1.0	100
	mITT - overall	106/3,721 (2.8)	150/3,720 (4.0)	0.69	0.54–0.89	0.003	1.2	84
Symptomatic VTE (symptomatic DVT + non-fatal PE + VTE-related death) + Major bleeding	mITT - overall	60/3,721 (1.6)	75/3,720 (2.0)	0.77	0.55–1.08	0.125	0.4	
	mITT - 80 mg	38/2,878 (1.3)	57/2,926 (1.9)	0.66	0.44–1.00	0.047	0.6	159
Symptomatic VTE + Major bleeding + All-cause mortality	mITT - Cohort 1	142/2,314 (6.1)	152/2,313 (6.6)	0.93	0.74–1.16	0.50	0.4	-
	mITT - Cohort 2	186/3,407 (5.5)	187/3,391 (5.5)	0.98	0.80–1.19	0.82	0	-
	mITT - overall	188/3,721 (5.1)	203/3,720 (5.5)	0.91	0.75–1.11	0.36	0.4	-
	mITT - 80 mg, Cohort 1	101/1,828 (5.5)	117/1,826 (6.4)	0.86	0.66–1.11	0.25	0.9	-
	mITT - 80 mg, Cohort 2	132/2,720 (4.9)	144/2,718 (5.3)	0.92	0.73–1.16	0.46	0.5	-
	mITT - 80 mg, overall	134/2,987 (4.5)	157/2,990 (5.3)	0.85	0.68–1.07	0.16	0.8	-
Symptomatic VTE + Major or CRNM Bleeding + All-cause Mortality	mITT - Cohort 1	194/2,314 (8.4)	177/2,313 (7.7)	1.09	0.90–1.32	0.40	-0.7	-
	mITT - Cohort 2	263/3,407 (7.7)	221/3,391 (6.5)	1.16	0.97–1.38	0.10	-1.2	-
	mITT - overall	271/3,721 (7.3)	237/3,720 (6.4)	1.12	0.94–1.32	0.21	-0.9	-
	mITT - 80 mg, Cohort 1	138/1,828 (7.5)	141/1,826 (7.7)	0.98	0.78–1.22	0.83	0.2	-
	mITT - 80 mg, Cohort 2	187/2,720 (6.9)	174/2,718 (6.4)	1.06	0.87–1.30	0.57	-0.5	-
	mITT - 80 mg, overall	194/2,987 (6.5)	187/2,990 (6.3)	1.02	0.84–1.25	0.82	-0.2	-
Primary Efficacy Outcome (asymp. & symp. DVT + non-fatal PE + VTE-related death) + Major bleeding + CRNM Bleeding Leading to Hospitalisation	mITT - Cohort 1	145/2,314 (6.3)	173/2,313 (7.5)	0.83	0.67–1.03	0.094	1.2	-
	mITT - Cohort 2	181/3,407 (5.3)	217/3,391 (6.4)	0.83	0.69–1.0	0.060	1.1	-
	mITT - overall	186/3,721 (5.0)	236/3,720 (6.3)	0.79	0.66–0.96	0.02	1.3	75

Post-hoc sub-group analyses

Subgroups with a lower inherent risk of bleeding and potentially a more positive benefit-risk profile for betrixaban were further explored by the applicant.

The first approach was the exclusion of patients who by protocol were considered to be at higher bleeding risk and for whom the dose of betrixaban was reduced from 80 mg to 40 mg. These were patients with severe renal impairment (CrCl < 30 ml/min) and those on potent P-gp inhibitors. The summary of the results in this sub-group are presented in **Table 35**.

Table 30. Summary of Efficacy and Safety, 80 mg Dose, PEOP-APEX Study

	Betrixaban n/N % (95% CI) [1]	Enoxaparin n/N % (95% CI) [1]	Relative Risk (95% CI) [2]	p-Value [3]	ARR (95% CI) [4]
Efficacy					
Primary Efficacy Outcome	120/2,426 4.95 (4.08, 5.81)	180/2,511 7.17 (6.16, 8.18)	0.697 (0.557, 0.872)	0.001	2.22 (0.89, 3.55)
First Secondary Efficacy Outcome	22/2,878 0.76 (0.45, 1.08)	41/2,926 1.40 (0.98, 1.83)	0.547 (0.327, 0.915)	0.020	0.64 (0.11, 1.17)
Second Secondary Efficacy Outcome	213/2,519 8.46 (7.37, 9.54)	281/2,612 10.76 (9.57, 11.95)	0.790 (0.666, 0.936)	0.006	2.30 (0.69, 3.91)
Safety					
Major Bleeds	15/2,986 0.50 (0.25, 0.76)	16/2,991 0.53 (0.27, 0.80)	0.939 (0.465, 1.896)	0.861	0.03 (-0.33, 0.40)
Major or CRNM Bleeds Leading to Hospitalisation	22/2,986 0.74 (0.43, 1.04)	22/2,991 0.74 (0.43, 1.04)	1.002 (0.556, 1.805)	0.996	0.00 (-0.43, 0.43)
Major or CRNM Bleeds	81/2,986 2.71 (2.13, 3.30)	49/2,991 1.64 (1.18, 2.09)	1.656 (1.166, 2.352)	0.004	-1.07 (-1.81, -0.34)

Note: The target population includes only the 80 mg subgroup of patients.

[1] Percentages and events rates are based on the total number of patients in each treatment group.

[2] Relative risk (betrixaban versus enoxaparin arm) represents the ratio of the proportions of patients who developed at least one event. The relative risk is stratified by entry criteria for the efficacy and net clinical benefit analyses.

[3] p-Values are based on the Mantel-Haenszel test stratified by entry criteria for efficacy and net clinical benefit analyses. p-Values are based on the Chi-Square Test or the Fisher's test if any expected cell count is less than 5 for the safety analyses.

[4] Absolute Risk Reduction (ARR) is calculated as Enoxaparin Event Rate – Betrixaban Event Rate.

The second approach consisted subjects receiving 80 mg dose of betrixaban who at the time of admission had at least one additional risk factor of VTE, including history of VTE, history of cancer, history of ischaemic stroke, chronic heart failure, obesity, or hormone replacement therapy. Note that this patient segment can be identified simply by taking a medical history and not by laboratory testing. The summary of the results in this sub-group are presented in **Table 36**.

Table 31. Summary of Efficacy and Safety, 80 mg dose, Patients with One of the Following Criteria: History of VTE, History of Cancer, History of Ischaemic Stroke, Chronic Heart Failure, Obesity, Hormone Replacement Therapy, PEOP

	Betrixaban n/N % (95% CI) [1]	Enoxaparin n/N % (95% CI) [1]	Relative Risk (95% CI) [2]	p-Value [3]	ARR (95% CI) [4]
Efficacy					
Primary Efficacy Outcome	74/1,370 5.40 (4.20, 6.60)	113/1,387 8.15 (6.71, 9.59)	0.659 (0.497, 0.874)	0.004	2.75 (0.87, 4.62)
First Secondary Efficacy Outcome	13/1,622 0.80 (0.37, 1.24)	27/1,641 1.65 (1.03, 2.26)	0.477 (0.247, 0.921)	0.024	0.84 (0.09, 1.60)
Second Secondary Efficacy Outcome	126/1,422 8.86 (7.38, 10.34)	174/1,448 12.02 (10.34, 13.69)	0.726 (0.584, 0.901)	0.004	3.16 (0.92, 5.39)
Safety					
Major Bleeds	9/1,682 0.54 (0.19, 0.88)	11/1,691 0.65 (0.27, 1.03)	0.823 (0.342, 1.980)	0.662	0.12 (-0.40, 0.63)
Major or CRNM Bleeds Leading to Hospitalisation	13/1,682 0.77 (0.35, 1.19)	17/1,691 1.01 (0.53, 1.48)	0.769 (0.375, 1.578)	0.472	0.23 (-0.40, 0.87)
Major or CRNM Bleeds	38/1,682 2.26 (1.55, 2.97)	31/1,691 1.83 (1.19, 2.47)	1.232 (0.771, 1.971)	0.382	-0.43 (-1.38, 0.53)

Note: The target population includes only the 80 mg subgroup of patients with at least one of the following: history of VTE, history of cancer, history of ischemic stroke, chronic heart failure, obesity, hormone replacement therapy.

[1] Percentages and events rates are based on the total number of patients in each treatment group.

[2] Relative risk (betrixaban versus enoxaparin arm) represents the ratio of the proportions of patients who developed at least one event. The relative risk is stratified by entry criteria for the efficacy and net clinical benefit analyses.

[3] p-Values are based on the Mantel-Haenszel test stratified by entry criteria for efficacy and net clinical benefit analyses. p-Values are based on the Chi-Square Test or the Fisher's test if any expected cell count is less than 5 for the safety analyses.

[4] Absolute Risk Reduction (ARR) is calculated as Enoxaparin Event Rate – Betrixaban Event Rate.

Missing data

In order to address issues of missing data, multiple imputation analysis, under two different underlying assumptions about the missing data was submitted by the applicant.

In the first analysis (**Table 37**), which assumed the missing data were missing at random , missing values of VTE were multiply imputed based on the predicted probability of a VTE in the assigned treatment arm, conditioning on key covariates.

In the second analysis(Table 38), using the jump-to-reference (JTC) approach, multiple imputation of missing values of VTE was based on the predicted VTE probability in the control arm, regardless of the assigned treatment.

Additional analysis including patient X were performed and obtained similar results (data not shown).

Table 32. Missing at Random Analysis: Multiple Imputation Assuming VTE Event Rates in the Treatment Arm to Which the Subject was Randomised Excluding Patient X

Cohort	Betrixaban n/N % (95% CI) [1]	Enoxaparin n/N % (95% CI) [1]	ARR (95% CI)	Relative Risk (95% CI) [2]	Relative Risk Reduction (95% CI)	p-Value [3]
Cohort 1	154/2,314 6.65 (5.53, 7.77)	190/2,313 8.21 (7.01, 9.41)	1.56 (-0.10, 3.22)	0.81 (0.64, 1.01)	0.19 (-0.009, 0.36)	0.112
Cohort 2	186/3,407 5.46 (4.64, 6.28)	234/3,391 6.88 (5.96, 7.80)	1.42 (0.20, 2.63)	0.79 (0.65, 0.97)	0.21 (0.032, 0.35)	0.042
Overall	192/3,721 5.15 (4.37, 5.92)	255/3,720 6.83 (5.96, 7.70)	1.69 (0.54, 2.84)	0.75 (0.62, 0.91)	0.25 (0.087, 0.38)	0.008

Table 33. Jump to Control Analysis: Multiple Imputation Assuming VTE Event Rates in the Enoxaparin Arm Excluding Patient X

Cohort	Betrixaban n/N % (95% CI) [1]	Enoxaparin n/N % (95% CI) [1]	ARR (95% CI)	Relative Risk (95% CI) [2]	Relative Risk Reduction (95% CI)	p-Value [3]
Cohort 1	160/2,314 6.89 (5.74, 8.03)	190/2,313 8.20 (6.99, 9.41)	1.31 (-0.35, 2.98)	0.84 (0.67, 1.04)	0.17 (-0.043, 0.33)	0.219
Cohort 2	193/3,407 5.65 (4.80, 6.50)	233/3,391 6.86 (5.96, 7.76)	1.21 (-0.02, 2.43)	0.82 (0.68, 1.00)	0.18 (-0.002, 0.32)	0.099
Overall	200/3,721 5.37 (4.56, 6.18)	255/3,720 6.84 (5.94, 7.73)	1.46 (0.28, 2.64)	0.78 (0.65, 0.95)	0.22 (0.047, 0.36)	0.027

[1] Estimated by combining multiply imputed datasets following Rubin's rules. The number of subjects with VTE was calculated by multiplying the imputed probability of VTE and the sample size in each treatment arm at each cohort.
[2] Relative risk of betrixaban arm vs enoxaparin arm.
[3] Analysed by Mantel-Haenszel Chi-square test. The CMH test statistic is pooled using the Wilson-Hilferty transformation.

Tipping Point Analysis with Multiple Imputation (assuming MNAR)

To assess the potential impact of higher rates of VTE in the betrixaban arm than expected under the MAR assumption, a tipping point analysis was implanted by the applicant employing multiple imputation to fit a pattern-mixture model for both observed and missing cases and assuming that data in the betrixaban arm are Not Missing At Random (MNAR).

The tipping point analysis in the overall mITT population and in Cohorts 1 are 2 are summarised in **Table 39**.

Table 34. Summary of Tipping point analyses in different analysis populations in the APEX study

	mITT		Cohort 2		Cohort 1	
	Betrixaban	Enoxaparin	Betrixaban	Enoxaparin	Betrixaban	Enoxaparin
N	3,685	3,689	3,377	3,364	2,314	2,313
Number of Patients with Missing Primary Outcome	603	539	559	491	400	357
Number of Patients with Evaluable Primary Outcome	3,082	3,150	2,818	2,873	1,914	1,956
Observed Number of Events	165	221	160	203	132	166
Observed Percentage of Subjects with VTE	5.4%	7.0%	5.7%	7.1%	6.9%	8.5%
Percentage of Subjects with VTE at Tipping Point	5.9%	7.0%	5.9%	7.1%	7.0%	8.5%
Imputed Number of Events at Tipping Point	216	259	200	238	163	196
Percentage of Subjects with VTE Among Those Missing Primary Efficacy Outcome at Tipping Point	8.4%	7.0%	7.2%	7.1%	7.7%	8.5%
Increase in VTE Events Compared to Observed	51	38	40	35	31	30

Summary of main study

The following tables summarise the efficacy results from the main study 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 35. Summary of Efficacy for trial 11-019 (APEX Study)

Title: Acute Medically Ill Prevention with Extended Duration Betrixaban Study (APEX)		
Study identifier	Study 11-019	
Design	Randomized, double-blind, parallel group, multicenter, multinational, active control superiority study	
	Duration of main phase:	30+5 days
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Superiority	
Treatments groups	Betrixaban	Betrixaban 80 mg after a 160 mg loading dose, duration 35 to 42 days, number randomized=3759
	Enoxaparin	Enoxaparin 40 mg SQ QD(20 mg SQ QD Enoxaparin if GFR<30) during 10+/-4 days, number randomized=3754
Endpoints and definitions	Primary efficacy endpoint	Composite endpoint : occurrence of any of: Asymptomatic proximal DVT (as detected by ultrasound), Symptomatic DVT (proximal or distal), Non-fatal PE, or VTE-related death , through Visit 3 (i.e. up to Day 47)

	First secondary efficacy endpoint	As primary endpoint except that only symptomatic events were included (VTE-related death, non-fatal PE and symptomatic DVT)
	Second secondary efficacy endpoint	Composite endpoint consistent with the primary endpoint except that all-cause mortality was included instead of only VTE-related death
Database lock	***11 March 2016***	
Results and Analysis		
Analysis description	**Analysis of the primary endpoint**	
Analysis population and time point description	Primary Efficacy Outcome Population (PEOP = all patients in the mITT population with available assessment of all components of the primary efficacy outcome endpoint.) in cohort 1, cohort 2 and overall population	

Descriptive statistics and estimate variability	Treatment group	Betrixaban	Enoxaparin
	Number of subject	3759 /1914 (randomized/PEOP Cohort1)	3754/1956 (randomized/PEOP Cohort 1)
	Primary endpoint, **primary** analysis in Cohort 1 of the PEOP (%)	6.90	8.49
	95% CI	5.76-8.03	7.25-9.72
	Primary endpoint in overall PEOP (%)	5.30	7.03
	95% CI	4.51-6.09	6.14-7.91
	First Secondary endpoint in Cohort 1 of FSEOP (%)	1.30	1.90
	95% CI	0.84-1.76	1.35-2.46
	First Secondary endpoint in overall FSEOP (%)	0.94	1.45
	95% CI	0.63-1.25	1.07-1.84
	Second Secondary endpoint in Cohort 1 of SSEOP (%)	11.52	12.85
	95% CI	10.13-12.91	11.41-14.30
	Second Secondary endpoint in overall SSEOP	9.18	10.85

	95% CI	8.19-10.18	9.79-11.91
Effect estimate per comparison	Primary endpoint, **primary** analysis in Cohort 1 of the PEOP	Comparison groups	Betrixaban vs Enoxaparin
		Absolute risk reduction (ARR)	1.59%
		Variability statistic	95% CI for ARR not provided
		P-value	0.054
	Primary endpoint in overall PEOP	Comparison groups	Betrixaban vs Enoxaparin
		ARR	1.73%
		Variability statistic	95% CI for ARR not provided
		Nominal p-value	0.006
	First Secondary endpoint, Cohort 1 FSEOP	Comparison groups	Betrixaban vs Enoxaparin
		ARR	0.61%
		Variability statistic	95% CI for ARR = -0.12, 1.33
		Nominal p-value	0.092
	First Secondary endpoint, overall FSEOP	Comparison groups	Betrixaban vs Enoxaparin
		ARR	0.51%
		Variability statistic	95% CI for ARR= 0.02, 1.00
		Nominal p-values	0.039
	Second Secondary endpoint, Cohort 1 SSEOP	Comparison groups	Betrixaban vs Enoxaparin
		ARR	1.33
		Variability statistic	95% CI for ARR not provided
		Nominal p-value	0.164
	Second Secondary endpoint, overall SSEOP	Comparison groups	Betrixaban vs Enoxaparin
		ARR	1.67
		Variability statistic	95% CI for ARR not provided
		Nominal p-values	0.024

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

Not applicable.

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	794/3716	1948/3716	602/3716

There was no modification of the treatment effect as a function of age (data not shown).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The development programme for Betrixaban included three phase II studies pertaining to indications that are approved for the other, already authorised, oral direct factor Xa inhibitors. Pharmacological and safety data can be derived from these studies but very limited conclusions regarding the efficacy of betrixaban in its proposed indication. For this purpose a large pivotal phase III study, the APEX study was conducted. APEX was a randomized, double-blind, parallel group, multi-centre, multi-national active-control superiority study for prevention of VTE in patients who are at risk due to acute medical illness. Betrixaban was administered over an extended duration (35 to 42 days) and the active control was 10 ± 4 days of parenteral Enoxaparin, the standard of care.

The objective of the APEX study was to demonstrate superiority of extended VTE prophylaxis with betrixaban vs standard of care prophylaxis with enoxaparin at reducing VTE (without an excessive increase in the risk of major bleeding). Patients were eligible if they were hospitalized for specified acute medical illness; acutely decompensated heart failure, acute respiratory failure in patients with chronic symptomatic lung disease, acute infection without septic shock, acute rheumatic disorders (including acute lumbar pain, sciatica, vertebral compression, rheumatoid arthritis, systemic lupus erythematosus) or acute ischemic stroke, had reduced mobility and had any one of the following risk factors for VTE: a. ≥ 75 years of age, or b. 60 through 74 years of age with D-dimer ≥ 2 x ULN, or c. 40 through 59 years of age with D-dimer ≥ 2 x ULN and a history of either VTE or cancer.

The critical place of D-dimer testing in the assessment of whether patients were eligible to the study and thus the definition of the study population was questioned by the CHMP. Elevated D-dimer levels are not an established risk factor in this clinical setting and it is not clear from the provided data to what extent the D-dimer estimations contributed to a relevant selection of patients at risk. The applicant considered that the predictive utility of D-dimer testing for the occurrence of VTE among acutely ill medical patients has been well-established. The CHMP's view however was that D-dimer testing is not used in clinical practice as a biomarker to identify high-risk patients for VTE, and therefore not a suitable method by which to determine the target population for betrixaban. Furthermore, several amendments of the inclusion and exclusion criteria were implemented during the course of the study. Approximately, half of the study population were included before the most significant, study amendment (Protocol Amendment 3 (04 June 2014)). This amendment had implications on the eligibility criteria regarding risk factors required in order to be included (age, D-dimer and other risk factors) and the statistical analysis strategy. These changes in the recruitment of patients in the trial and the uncertainties around the predictive value of D-dimer testing makes it difficult to define the target population that truly would benefit from prolonged treatment with betrixaban with sufficient certainty. The appropriate target population for betrixaban is further discussed under "Efficacy data and additional analyses.

The primary outcome was a composite endpoint and constituted of the occurrence of any of the following events through Visit 3 (i.e. up to Day 47): Asymptomatic proximal DVT (as detected by ultrasound), Symptomatic DVT (proximal or distal), Non-fatal PE, or VTE-related death. The primary efficacy outcome selected was consistent with current EMA guidelines, with the exception that it included VTE-Related death instead of all-cause mortality which is recommended for superiority trials. However the composite endpoint of asymptomatic proximal DVTs, symptomatic VTEs or all-cause mortality was included as a secondary endpoint. Therefore the selection of endpoints to assess the efficacy of betrixaban in the APEX trial was considered appropriate.

Efficacy data and additional analyses

In the APEX study a total of 7,441 subjects were treated with study drug (3,721 and 3,720 in the betrixaban and enoxaparin treatment groups, respectively), and comprised the mITT analysis set and 6,286 subjects were included in the Primary Efficacy Outcome Population analysis set (PEOP).

Superiority vs standard of care with enoxaparin was not demonstrated for betrixaban. The event rates (95% CI) % for step 1 in the primary analysis in Cohort 1 (patients with (D-Dimers ≥2 ULN)) was 8.5 (7.3-9.7) % in the Enoxaparin arm and 6.9 (5.8-8.0) % in the betrixaban arm (p=0.054). The applicant argued that the alternative analysis, including an additional patient (Patient X) treated with enoxaparin and who qualified as meeting the primary efficacy endpoint in Cohort 1 should form the basis for assessing Cohort 1 in the hierarchical gate-keeping procedure. This analysis demonstrated a statistically significant reduction in the pre-specified primary efficacy outcome favouring the betrixaban strategy in Cohort 1 (RRR of 19.8%, p = 0.048).

The CHMP accepted that this analysis showed a borderline statistical significance but expressed concerns over putting the emphasis on an alternative analysis of the predefined outcome as there are always numerous other possibilities to analyse the primary outcome. Hence there is a general requirement that the analysis of the primary endpoint should be unambiguously pre-specified, in order to avoid selective reporting. More importantly, in a single pivotal study setting, robustness of the results should not be affected by the inclusion or exclusion of one or two patients and would be expected to be beyond the nominal significance level of 0.05.

Additional analyses of the primary efficacy outcome, both pre-specified and post hoc, in patients in Cohort 1 were conducted and presented by the applicant. The results of these analyses were overall in line with the primary pre-specified analysis of the primary endpoint albeit with some variations in point estimate, confidence intervals and p-values. The event rate (95% CI) % for the primary efficacy analysis in the overall primary efficacy population was 5.3 (4.5-6.1) % for betrixaban and 7.0 (6.1-7.9) % for the comparator (nominal p-value=0.006).

The applicant provided a number of arguments for proceeding to step 2 and 3 of the hierarchical testing procedure despite the non-significant result in step 1. In Cohort 2 and the overall population, the p-values for the comparison between betrixaban and the comparator were lower than in Cohort 1 (and below 0.05), however the ARR using the point estimate was similar in Cohort 1, Cohort 2 and the overall population. The event rate (95% CI) % for the primary efficacy analysis in the overall primary efficacy population was 5.3 (4.5-6.1) % for betrixaban and 7.0 (6.1-7.9) % for the comparator (nominal p-value=0.006). Overall, the outcome of the secondary analysis was generally in line with the outcome of the primary analysis.

The outcome of the pre-specified subgroups analysis of the primary efficacy outcome in Cohort 1 was generally consistent with the outcome of in the overall population. There were some concerns regarding the subgroup analysis. In the analysis of the primary efficacy outcome by dosing criteria, patients with neither severe renal insufficiency nor need for a strong P-gp inhibitor randomized to 80 mg betrixaban had an event rate % of 6.3 % vs. 8.4% in patients receiving enoxaparin (nominal p = 0.026). For patients with severe renal insufficiency, the event rate was 10.2% in the betrixaban group vs 12.7% in the enoxaparin group (nominal p=0.598). For patients on strong P-gp inhibitors, the event rate was 8.5 in the betrixaban group vs 7.9 in the enoxaparin group (nominal p=0.767).

The first secondary efficacy analysis included only symptomatic events. The event rates (95% CI) % for Cohort 1 in the analysis of the first secondary efficacy endpoint was 1.3 (0.8-1.8) % for betrixaban and 1.9 (1.4-2.5) % for the comparator (nominal p-value 0.092). The event rates (95% CI) % were 0.9 (0.6-1.3) % for betrixaban and 1.5 (1.1-1.8) % for the comparator in the overall population (nominal p-value= 0.039)

The second secondary efficacy endpoint is of special interest since it is the analysis that is recommended as the primary efficacy outcome in this kind of superiority trial according to EMA guideline. It is of value since it cannot be excluded that some of the deaths that were classified as not VTE-related by the independent CEC were in fact VTE-related (it is not explicitly stated in the study report that adjudication of deaths always included for example autopsies). As the number of deaths were rather similar in the two treatment arms, the absolute difference in event rate between the groups in the overall population is approximately the same for the second secondary endpoint as for the primary endpoint but the p-value is affected. The event rate (95% CI) for the second secondary efficacy outcome in Cohort 1 was 11.5 (10.1-12.9) % for betrixaban and 12.9 (11.4-14.3) % for the comparator (nominal p-value=0.164).The event rate (95% CI) % for the second secondary endpoint in the overall population is 9.2 (8.2-10.2) % and 10.9 (9.8-11.9) % (nominal p-value=0.024).

Regarding the different components of the primary endpoint (also considered secondary endpoints); the rates in the PEOP, Cohort 1 for Betrixaban vs the comparator was 5.5% vs 6.6% for at least one asymptomatic event, 0.7% vs 1.0% for at least one symptomatic DVT, 0.3% vs 0.9% for at least one non-fatal PE and 0.6% in both groups for VTE-related deaths.

The net clinical benefit was a tertiary/exploratory outcome in the APEX study. It was defined as the composite of the primary efficacy outcome plus major bleeding. As this is not in line with the CHMP guideline or with other contemporary studies, the applicant was requested to recalculate the net clinical benefit as: 1) The composite of symptomatic events, all cause death and major bleeding, 2) The composite of symptomatic events, all cause death and major and CRNM bleedings. The first analysis led to an ARR of 0.4% for Cohort 1, 0% for Cohort 2 and 0.4% for the overall population. The second analysis resulted in an ARR for Cohort 1, Cohort 2 and the overall population, favouring the comparator. The applicant argued that inclusion of CRNM bleeds in NBC gives these events a similar weight with events that cause death or irreversible harm. These arguments were acknowledged. However, the CHMP noted that CRNM bleedings had also been included in the evaluation of the net clinical benefit in the MAGELLAN study, leading to a negative benefit–risk ratio (although major bleedings were increased in the rivaroxaban group compared to the enoxaparin group in this study). The CHMP agreed that both definitions of "net clinical benefit" have different weaknesses. However, even with the most favourable for betrixaban analysis, the benefits compared to enoxaparin treatment appeared to be marginal.

The CHMP also noted that, there was no evidence of an advantage of betrixaban over enoxaparin in patients randomized to receive 40 mg betrixaban (patients with severe renal insufficiency and patients receiving a strong P-gp inhibitor) in the APEX study. In the analysis by dosing criteria, patients with neither severe renal insufficiency nor need for a strong P-gp inhibitor randomized to 80 mg betrixaban had an event rate of 6.3% vs. 8.4% in patients receiving Enoxaparin (nominal p = 0.026). For patients with severe renal insufficiency, the event rate was 10.2% in the betrixaban group (11/108) vs 12.7% in the Enoxaparin group (10/79) (nominal p=0.598). For patients on strong P-gp inhibitors, the event rate was 8.5% (29/342) in the betrixaban group vs 7.9% (28/356) in the Enoxaparin group (nominal p=0.767). During the course of the assessment procedure, it was decided that betrixaban should not be used in patients with severe renal impairment or patients concomitantly using potent Pgp-inhibitors and it was thus agreed that the 40 mg strength should be withdrawn.

The applicant accepted this restriction in the intended use of betrixaban, and consequently explored subgroups with a lower inherent risk of bleeding and potentially a more positive benefit-risk profile for betrixaban. Further to this restriction, the applicant amended the proposed indication for betrixaban to the prophylaxis of VTE in adults hospitalised for an acute medical illness (such as acute heart failure, respiratory insufficiency, severe infections, acute rheumatic diseases, or ischemic stroke) who are at risk for thromboembolic complications due to restricted mobility and other risk factors for VTE.

In the first explored subgroup, the applicant removed patients who per protocol were considered to be at higher bleeding risk i.e. the ones for which the dose of betrixaban was reduced from 80 mg to 40 mg. The applicant stated that removal of the 40 mg group results in a target population that has a benefit of excluding the most vulnerable patients with the highest bleeding risk, and which includes approximately two-thirds of the overall mITT population.

The CHMP acknowledged that that the ARR for the Primary Efficacy Outcome in this sub-group (2.2%) was more in favour of betrixaban compared to the whole population (1.72%). Moreover, there is a reduction in the difference (-1.07%, compared to -1.53%) of major or CRNM in this subgroup, compared to the whole population. Nevertheless, the difference in absolute numbers for both the efficacy and safety result in this subgroup, compared the overall population, is not large.

The second explored subgroup consisted of patients receiving 80 mg dose of betrixaban who at the time of admission had at least one additional risk factor of VTE, including history of VTE, history of cancer, history of ischaemic stroke, chronic heart failure, obesity, or hormone replacement therapy. This subgroup corresponds to less than half of the subjects in the overall PEOP of the APEX trial. The ARR for the primary efficacy endpoint in this subgroup was observed to be numerically larger than what was observed in the first explored subgroup. Moreover, the increase in major plus CRNM bleeding in the betrixaban group (compared to enoxaparin) was numerically smaller than the one observed in the other subgroup. However, the limitations of a subgroup post hoc analysis clearly restrict the value of this subgroup as a target population for betrixaban.

A large number of the randomised patients in both treatment groups of the APEX study were not included in the primary efficacy population due to the lack of evaluable ultrasound results between Days 32 and 47 (and no symptomatic event). This number was higher in the betrixaban group than in the comparator group. If the incidence of asymptomatic thrombosis was higher in these subjects with missing ultrasounds compared to those included in the efficacy analysis, this would reduce the observed numerical difference in favour of betrixaban between the groups.

The applicant acknowledged the potential for informative censoring due to an imbalance in rates of missing CUS results across treatment arms with 16.4% in the betrixaban arm and 14.7% in the enoxaparin arm excluded from the PEOP.

This is an important concern as illustrated by the impact one patient (including/excluding patient X) may have on the strength of statistical evidence and hence the interpretation of the APEX study outcome. The initially performed mITT analysis (including all randomised except for those subjects who did not receive any treatment) implied an implicit outcome imputation of no event and given the imbalance in subjects with missing data, favoured betrixaban. To address this issue, a number of sensitivity analyses were performed by the applicant to impute the missing data.

In the first analysis, missing values of VTE were imputed based on the predicted probability of a VTE in the assigned treatment arm, conditioning on key covariates. In the second analysis, using the jump-to-reference (JTC) approach, multiple imputation of missing values of VTE was based on the predicted VTE probability in the control arm, regardless of the assigned treatment. While the first is based on the assumption of missing at random (MAR), the second is conservative under the assumption of a true difference in favour of betrixaban but neither approach will capture the scenario where failure to show up for the CUS is related to having the outcome of interest.

In the MAR analysis (excluding patient X) the results were the following; for Cohort 1: ARR = 1.6% and p = 0.11, for Cohort 2: ARR =1.4% and p = 0.042 and in the overall population: ARR = 1.7% and p = 0.008. The outcome of the MAR analysis is thus quite similar to the outcome in the primary analysis of the primary endpoint (for Cohort 1 ARR=1.6% and p=0.054, for Cohort 2 ARR=1.4% and p=0.029, for the overall population ARR=1.7% and p=0.006). In the JTC analysis (excluding patient X) the results were the following; for Cohort 1: ARR= 1.31 and p-value=0.219, for Cohort 2: AR=1.21 and p-value= 0.099, for the overall population: AR= 1.46 and p-value=0.027. Thus, in this more conservative analysis, the estimates of the treatment difference were smaller compared to the outcome in the primary analysis of the primary endpoint.

Irrespective of analysis (MAR, JTC) the outcome in Cohort 1 was statistically inconclusive. In the MAR analysis the p-value for the treatment difference in cohort 2 was <0.05 but without being statistically compelling and in the second analysis the corresponding p-value was >0.05. In both the analyses the comparison based on the overall population was nominally statistically significant, more convincingly so, as could be expected, in the first MAR analysis (p=0.008) compared to in the second (JTC; p=0.027). However, irrespective of analysis (cohort 1, cohort 2, overall population), the point estimate for the RR difference between betrixaban and enoxaparin was shown to be fairly consistent, ranging between 0.75 to of 0.84; the maximum calculated upper limit of any 95% CI for the RR was 1.04.

The applicant also carried out a tipping point analysis using an approach that employs multiple imputation and increasing the estimated rate of VTE in the betrixaban arm until the tipping point is reached where the superiority of betrixaban can no longer be considered significant at the 5% level. The proportion of VTEs at the tipping point in the missing outcome patients can then be compared to the observed proportion of VTEs and the likelihood of occurrence assessed. A finding that the resulting imputed VTE rate is highly unlikely would confirm the robustness of the observed results and would indicate that the original findings are robust to assumptions about the missing data. The outcome of these analyses are that in Cohort 1, the tipping point occurs when the percentage of VTEs in the missing data from the betrixaban arm is 7.7% (compared to observed rate 6.9%), in Cohort 2 the tipping point occurs when the percentage of VTEs in the missing data from the betrixaban arm is 7.2% (observed rate 5.7%) and in the overall mITT population the tipping point occurs when the percentage of VTE events for subjects with missing data in the betrixaban arm is 8.4% (observed rate 5.4%).

In response to the LoQs, the issue of missing data was explored through sensitivity analysis based on the mITT analysis population using different statistical approaches to handle the missing assessments; the outcome of these analysis confirm CHMP's view that the results, especially in Cohort 1 (which was the population in which the primary endpoint was to be tested according to the predefined statistical testing procedure) was not robust.

According to the EMA guideline, "*Points to consider on application with 1. Meta-analyses; 2.One pivotal study",* reasons where it is prudent to plan for more than one phase III study include for example limited/unconvincing phase I and phase II data and a therapeutic area with a history of failed studies. In cases where the confirmatory evidence is provided by one pivotal study only, this study has to be exceptionally compelling and in the regulatory evaluation special attention will be paid to internal and external validity, data quality, internal consistency, clinical relevance and the degree of statistical significance; a statistical evidence considerably stronger than $p<0.05$ is usually required accompanied by narrow confidence intervals.

Despite the various sensitivity analyses performed by the applicant and which would appear to increase the difference in treatment effect of betrixaban compared to enoxaparin, the study is, strictly, formally failed. Only in ignoring the pre-specified testing strategy (or accepting the alternative analysis including patient X) can the outcome be considered statistically significant and even then it can be questioned whether the strength of the level of statistical evidence is sufficiently compelling in the single pivotal setting. Thereby, support from other sources of information becomes even more critical.

Regarding external support for the use of betrixaban and for the proposed duration of treatment in the proposed target population, the applicant points out that prior studies of extended VTE prophylaxis in this indication (ADOPT, MAGELLAN, EXCLAIM), clearly demonstrated that a substantial rate of VTE occurs in patients beyond the standard duration of VTE prophylaxis and thereby provide external support for a 35 to 42 day treatment period in the proposed target population. However, the CHMP noted that a positive overall Benefit Risk with extended anticoagulation treatment in these studies was not demonstrated. In ADOPT, an extended course of thromboprophylaxis with apixaban in medically ill patients was not proven to be superior to a shorter course with enoxaparin, and apixaban was associated with significantly more major bleeding events than enoxaparin (Goldhaber et al, NEJM 2011). In MAGELLAN, rivaroxaban was indeed non-inferior to enoxaparin for standard-duration thromboprophylaxis and extended-duration rivaroxaban reduced the risk of venous thromboembolism but rivaroxaban was associated with an increased risk of bleeding compared to enoxaparin (Cohen et al, NEJM 2013). In EXCLAIM, extended-duration enoxaparin reduced VTE incidence compared with placebo but enoxaparin increased major bleeding events (Hull et al, Ann Intern Med, 2010). In this context, the CHMP considered that the level of support for extended anticoagulation treatment in the target population in general and betrixaban in particular is very limited. The CHMP therefore concluded that in a therapeutic area with a history of failed studies/failures to confirm seemingly convincing results, that even if the outcome of the APEX study could be regarded as compelling, a confirmatory study would still be needed.

Additional expert consultation

The CHMP convened a Cardiovascular Scientific Advisory Group (SAG) in order to provide their views on the following issues:

1. Please discuss the clinical relevance of the magnitude of the treatment effect of Betrixaban as documented in the APEX study (primary and secondary endpoints), in particular in terms of absolute risk reduction.

Also discuss if there is an unmet medical need, including the need for a longer treatment duration, in the proposed target population as well as previous knowledge on the risk for thrombosis in patients that suffer from acute medical illness.

The Group considered that the reported reduction in the incidence of the events included in the composite primary endpoint (asymptomatic DVT, symptomatic proximal or distal DVT, PE and VTE-related death) in the APEX study are of clinical relevance even though it was noted that the effect size was lower than that which the study was powered to detect.

However the SAG expressed concerns over the robustness of the reported results and that due to the design of the study and the statistical analysis used it would be difficult to determine with certainty the exact target population that would be expected to benefit from betrixaban treatment.

Betrixaban was compared to Enoxaparin through a closed testing, gate-keeping procedure, which however failed to return statistically compelling results at the first stage in patients with elevated D dimers who were expected to constitute the patients at highest risk for DVTs. The Group therefore considered that there is considerable uncertainty around the subsequent analyses performed by the company.

In addition, the application is based on a single pivotal study. In such a setting, robustness of the results should not be affected by the inclusion or exclusion of one or two patients and would be expected to be beyond the nominal significance level of 0.05. The SAG noted that nominal statistical significance was achieved with the inclusion of an additional patient. However, the SAG also noted the imbalance in the patients between the treatment groups excluded from the primary analysis due to lack of ultrasound data which could potentially bias the results in favour of Betrixaban.

There was general agreement that there is unmet medical need for prolonged thromboprophylaxis in acutely ill medical patients. It was acknowledged that the risk of thrombotic events for patients requiring anticoagulation extends beyond 10-14 days. Importantly the Group noted that this risk could be particularly relevant for patients who are discharged early, i.e. after 4-5 days, and who as a result may discontinue their anticoagulant prophylaxis on discharge. The concept to extend the thromboprophylactic treatment beyond 14 days is attractive in principal but risks must be carefully considered.

2. **Please discuss the importance of the increased risk of "clinically relevant bleedings" associated with Betrixaban treatment in the studied population. What impact may this have in clinical practice and how does it affect the clinical utility of the drug?**

   What measures can be undertaken to minimize the bleeding risks induced by the proposed regimen?

   The Group noted that any prolongation of prophylactic therapy would most likely increase the risk of bleedings, in line with the reported results from the APEX study.

   The Group expressed their concerns over the increased incidence of CRNMBs in patients treated with Betrixaban and considered that these could limit the clinical utility of the product, which is intended in a frail and primarily elderly population. The group also noted that such events could also lead to treatment discontinuations which could have a detrimental effect on the management of such patients if occurring early in the period currently protected by subcutaneous treatment.

   Although the safety results seem to be similar to the other DOACs, the Group also noted that some of the properties of the drug, such as significant influence of food intake and a long half- life could further impact on the risk of bleeding side effects.

The Group expressed further concerns about the clinical importance of CRNMBs, taking into account the anatomical location of the bleedings and that the majority of events were reported as SAEs. The Group emphasised the clinical importance of such events which could lead to hospitalisation or premature discontinuation of anti-coagulation treatment. The group agreed that it was important to know whether the bleedings occurred during the period that the patient was already hospitalised i.e. before discharge and whether anticoagulant therapy was discontinued. Additional concerns were raised that outside a clinical trial, in a real-world setting where patients are not followed up as intensively, bleedings after discharge could be expected to have a more profound clinical impact and sequelae.

The Group was not able to propose further measures to minimise this risk in addition to what was already being proposed by the applicant.

3. **Discuss if an appropriate target population for Betrixaban can be identified in light of the totality of data from the APEX study taking into account the studied population (e.g. the requirement for D-dimer testing)**

The Group felt that the D-dimer test is not useful in defining the target population. Data presented by the applicant, that central D-Dimer testing is more useful than local laboratory testing are irrelevant in the clinical setting.

Many further aspects diminishing the value of D-Dimer testing like age dependency, unclear value in patients with infectious diseases, unclear upper limit of normal values etc. have been brought up. Also it was felt that the intended medication should not trigger a D-Dimer test that is currently only done in a small minority of inpatients.

The Group noted that there are several predictive methods that have been designed for assessing the risk of VTE such as the Padua prediction score. However, it was emphasised that validation of these methods is lacking in general and specifically in the APEX study and therefore cannot currently be used in determining an appropriate target population for Betrixaban.

In view of the uncertainties around the efficacy of the product as summarised in the response to Question 1 but also the observed increased risk of bleedings the Group was unable to robustly identify additional patient characteristics which could be used in defining the most appropriate target population for Betrixaban.

2.5.4. Conclusions on the clinical efficacy

The results of the APEX study showed a positive trend for the prevention of thrombotic events in patients treated with betrixaban compared to those treated with enoxaparin for the proposed posology (extended prophylaxis) and indication (that included patients hospitalised for an acute medical illness). However, these results were not considered statistically robust and even failed (or at best, with the inclusion of patient X just passed) the pre-specified gate-keeping procedure that sequentially, in a hierarchal order, tested the primary and secondary efficacy composite outcome hypothesis in each of the three defined cohorts of the study. There are additional concerns over the criteria by which patients were recruited in the trial and missing data which cast further doubts on the robustness of the reported results.

For an application that is based on a single pivotal study, and with a history of failed trials with other similar products in the applied indication and a product with no clinical data in other indications, the evidence of efficacy of betrixaban for the prevention of DVT cannot be considered established.

2.6. Clinical safety

Patient exposure

A total of 4,969 subjects including patient and healthy volunteer subjects were exposed to at least one dose of betrixaban in Phase I to III studies. Safety data presented in this report will be limited to the Phase III study, as the Phase II studies relate to indication different to the one applied for with this application.

In the APEX study (pivotal study for this application), 3,716 acutely ill medical patients at risk of VTE were exposed to orally administered betrixaban and an equal number were exposed to the standard of care, active control agent, short term, subcutaneously administered enoxaparin. Of the 3,716 patients in the betrixaban group, 2,986 received 80 mg QD after a single loading dose of 160 mg, and 730 received 40 mg QD after a single loading dose of 80 mg.

Paient exposure in the APEX study according to the cohorts defined in this study is presented in **Table 41**.

To be eligible for enrolment, patients were required to present with at least one of the primary causes of acute hospitalization / primary risk criteria (i.e., acutely decompensated heart failure, acute respiratory failure, acute infection, acute rheumatic disorders, or acute ischemic stroke). A summary of the number and percent of patients in the Randomized Population with each primary risk criterion as well as other risk factors is provided in **Table 42**.

Demographic and Baseline characteristics were generally similar for patients in the PEOP overall and in Cohort 1 and Cohort 2 of the PEOP as well as for patients in the Safety Population overall and in Cohort 1 and Cohort 2 of the Safety Population as compared to the Randomized Population. Medical history at Baseline was generally similar for patients in the PEOP overall and in Cohort 1 and Cohort 2 of the PEOP as well as for patients in the Safety Population overall and in Cohort 1 and Cohort 2 of the Safety Population as compared to the Randomized Population. A small imbalance was noted for the patients with atrial fibrillation (15.9 and 17.3% for the betrixaban and enoxaparin groups respectively).

Table 36. Patient exposure to betrixaban and enoxaparin in the APEX study

	Cohort 1		**Cohort 2**		**Overall**	
	Betrixaban (N=2,311)	**Enoxaparin** (N=2,310)	**Betrixaban** (N=3,402)	**Enoxaparin** (N=3,387)	**Betrixaban** (N=3,716)	**Enoxaparin** (N=3,716)
Duration of Active Drug Exposure (days) [1]						
N	2,311	2,310	3,402	3,387	3,716	3,716
Mean (SD)	32.4 (11.28)	10.0 (4.97)	32.5 (11.08)	9.9 (4.90)	32.7 (10.87)	9.9 (4.84)
Median	36.0	9.0	36.0	9.0	36.0	9.0
Q1, Q3	34.0, 39.0	7.0, 14.0	34.0, 39.0	7.0, 13.0	34.0, 39.0	7.0, 13.0
Min, Max	1, 54	1, 45	1, 54	1, 45	1, 54	1, 45
Number of Patients with Duration of Active Drug Exposure n (%) [2]						
At Least 1 Day	2,311 (100.0)	2,310 (100.0)	3,402 (100.0)	3,387 (100.0)	3,716 (100.0)	3,716 (100.0)
At Least 6 Days	2,154 (93.2)	2,119 (91.7)	3,180 (93.5)	3,108 (91.8)	3,490 (93.9)	3,423 (92.1)
At Least 10 Days	2,080 (90.0)	1,077 (46.6)	3,071 (90.3)	1,529 (45.1)	3,372 (90.7)	1,685 (45.3)
At Least 14 Days	2,030 (87.8)	589 (25.5)	3,001 (88.2)	838 (24.7)	3,295 (88.7)	906 (24.4)
At Least 21 Days	1,954 (84.6)	62 (2.7)	2,896 (85.1)	86 (2.5)	3,184 (85.7)	90 (2.4)
At Least 28 Days	1,918 (83.0)	45 (1.9)	2,838 (83.4)	63 (1.9)	3,124 (84.1)	67 (1.8)
At Least 35 Days	1,692 (73.2)	18 (0.8)	2,511 (73.8)	24 (0.7)	2,763 (74.4)	25 (0.7)
At Least 42 Days	140 (6.1)	2 (< 0.1)	200 (5.9)	2 (< 0.1)	216 (5.8)	2 (< 0.1)
At Least 47 Days	26 (1.1)	0	33 (1.0)	0	36 (1.0)	0
At Least 50 Days	4 (0.2)	0	4 (0.1)	0	5 (0.1)	0

Notes: One patient was randomised to Betrixaban group but took active Enoxaparin. This patient is summarised under the Enoxaparin column.

[1] *The duration of Betrixaban exposure is calculated as last dose date — first dose date + 1. The duration of Enoxaparin exposure, including both double-blind study and also open label Enoxaparin administered before randomisation, is calculated as last dose date — first dose date + 1.*

Table 37. Cause of Acute Hospitalization / Primary Risk Criteria and Other Risk Factors – Randomized Population-APEX Study

	Betrixaban (N=3,759) n (%)	Enoxaparin (N=3,754) n (%)	Total (N=7,513) n (%)
Primary Risk Criteria for VTE Documented as the Cause of the Acute Hospitalization *			
Acutely Decompensated Heart Failure	1,677 (44.6)	1,672 (44.5)	3,349 (44.6)
Acute Respiratory Failure	448 (11.9)	474 (12.6)	922 (12.3)
Acute Infection Without Septic Shock	1,112 (29.6)	1,058 (28.2)	2,170 (28.9)
Acute Rheumatic Disorders	109 (2.9)	117 (3.1)	226 (3.0)
Acute Ischemic Stroke	411 (10.9)	432 (11.5)	843 (11.2)
Acutely Decompensated Heart Failure	1,677 (44.6)	1,672 (44.5)	3,349 (44.6)
Acute Respiratory Failure	448 (11.9)	474 (12.6)	922 (12.3)
Acute Infection Without Septic Shock	1,112 (29.6)	1,058 (28.2)	2,170 (28.9)
Acute Rheumatic Disorders	109 (2.9)	117 (3.1)	226 (3.0)
Acute Ischemic Stroke	411 (10.9)	432 (11.5)	843 (11.2)

Risk Factors			
Previous History of VTE (DVT Or PE) or Superficial Venous Thrombosis	312 (8.3)	296 (7.9)	608 (8.1)
Obesity (BMI > 35)	679 (18.1)	734 (19.6)	1413 (18.8)
Previous Documented Chronic Venous Insufficiency or Severe Varicosis of the Lower Extremity	702 (18.7)	690 (18.4)	1392 (18.5)
Lower Extremity Paresis or Hemiparesis or Hemiparalysis	294 (7.8)	277 (7.4)	571 (7.6)
Hormone Therapy (antiandrogen, estrogen, progesterone or Selective Estrogen Receptor Modulators [SERMS])	43 (1.1)	31 (0.8)	74 (1.0)
History of Cancer Excluding Non-Melanoma Carcinoma of the Skin	466 (12.4)	443 (11.8)	909 (12.1)
Chronic Heart Failure (NYHA Class III or IV)	853 (22.7)	865 (23.0)	1,718 (22.9)
Chronic Respiratory Failure	933 (24.8)	893 (23.8)	1,826 (24.3)
Active Collagen Vascular Disease Associated with Limited Mobility (e.g., isolated Sicca Syndrome will not qualify)	93 (2.5)	93 (2.5)	186 (2.5)
Acute Infectious Disease Contributing to Current Hospitalization	602 (16.0)	620 (16.5)	1,222 (16.3)
Current Concomitant Use of Erythropoeisis Stimulating Agents	4 (0.1)	3 (< 0.1)	7 (< 0.1)
Inherited or Acquired Thrombophilia	3 (< 0.1)	5 (0.1)	8 (0.1)
Number of Risk Factors			
0	1,007 (26.8)	993 (26.5)	2,000 (26.6)
1	1,225 (32.6)	1,258 (33.5)	2,483 (33.0)
2	992 (26.4)	962 (25.6)	1,954 (26.0)
3	391 (10.4)	411 (10.9)	802 (10.7)
4	120 (3.2)	111 (3.0)	231 (3.1)
> 4	24 (0.6)	18 (0.5)	42 (0.6)

Adverse events

In Phase III patients the overall incidence of TEAEs in the betrixaban group was similar to that in the enoxaparin group in the overall Safety Population as well as in Cohorts 1 and 2. Patients in the betrixaban group had higher incidence of TEAEs considered to be possibly or probably related to treatment (8.2% for betrixaban vs. 6.2% for enoxaparin); this trend was mirrored in Cohorts 1 and 2.

The most common adverse events in the APEX Phase III study are presented in **Table 43**.

Table 38. Frequent (> 1% in Either Treatment Group of Overall Safety Population) Treatment Emergent Adverse Events by Preferred Term, Sorted by Overall Betrixaban - Safety Population, APEX Study

	Cohort 1		Cohort 2		Overall	
Preferred Term	**Betrixaban** (N=2,311) **n** (%)	**Enoxaparin** (N=2,310) **n** (%)	**Betrixaban** (N=3,402) **n** (%)	**Enoxaparin** (N=3,387) **n** (%)	**Betrixaban** (N=3,716) **n** (%)	**Enoxaparin** (N=3,716) **n** (%)
Cardiac Failure	82 (3.5)	73 (3.2)	119 (3.5)	90 (2.7)	127 (3.4)	98 (2.6)
Urinary Tract Infection	80 (3.5)	56 (2.4)	116 (3.4)	84 (2.5)	123 (3.3)	87 (2.3)
Constipation	74 (3.2)	62 (2.7)	108 (3.2)	96 (2.8)	110 (3.0)	102 (2.7)
Headache	43 (1.9)	37 (1.6)	66 (1.9)	54 (1.6)	74 (2.0)	59 (1.6)
Hypokalaemia	67 (2.9)	60 (2.6)	88 (2.6)	78 (2.3)	93 (2.5)	84 (2.3)
Chronic Obstructive Pulmonary Disease	47 (2.0)	47 (2.0)	82 (2.4)	72 (2.1)	89 (2.4)	81 (2.2)
Hypertension	61 (2.6)	49 (2.1)	85 (2.5)	71 (2.1)	89 (2.4)	80 (2.2)
Insomnia	61 (2.6)	58 (2.5)	83 (2.4)	80 (2.4)	87 (2.3)	89 (2.4)
Pneumonia	51 (2.2)	69 (3.0)	72 (2.1)	93 (2.7)	79 (2.1)	99 (2.7)
Nausea	47 (2.0)	37 (1.6)	65 (1.9)	52 (1.5)	67 (1.8)	56 (1.5)
Diarrhoea	51 (2.2)	40 (1.7)	60 (1.8)	55 (1.6)	64 (1.7)	61 (1.6)
Haematuria	42 (1.8)	20 (0.9)	60 (1.8)	25 (0.7)	62 (1.7)	28 (0.8)
Atrial Fibrillation	36 (1.6)	73 (3.2)	60 (1.8)	99 (2.9)	61 (1.6)	106 (2.9)
Epistaxis	40 (1.7)	14 (0.6)	52 (1.5)	24 (0.7)	58 (1.6)	24 (0.6)
Renal Cyst	39 (1.7)	26 (1.1)	53 (1.6)	43 (1.3)	55 (1.5)	47 (1.3)
Anaemia	36 (1.6)	24 (1.0)	51 (1.5)	31 (0.9)	52 (1.4)	33 (0.9)
Deep Vein Thrombosis	42 (1.8)	80 (3.5)	44 (1.3)	93 (2.7)	45 (1.2)	96 (2.6)
Mitral Valve Incompetence	29 (1.3)	29 (1.3)	35 (1.0)	44 (1.3)	41 (1.1)	50 (1.3)
Oedema Peripheral	28 (1.2)	13 (0.6)	39 (1.1)	16 (0.5)	40 (1.1)	19 (0.5)
Tricuspid Valve Incompetence	31 (1.3)	25 (1.1)	37 (1.1)	38 (1.1)	39 (1.0)	41 (1.1)
Renal Failure	23 (1.0)	31 (1.3)	32 (0.9)	41 (1.2)	33 (0.9)	42 (1.1)
Vomiting	16 (0.7)	32 (1.4)	24 (0.7)	37 (1.1)	25 (0.7)	39 (1.0)
Ischaemic Stroke	15 (0.6)	29 (1.3)	21 (0.6)	39 (1.2)	21 (0.6)	40 (1.1)

Serious adverse event/deaths/other significant events

Bleeding

Major bleedings (as defined by ISTH) were clinically overt bleedings that were associated with:

- Bleeding associated with a reduction in hemoglobin of at least 2 g/dl or leading to a transfusion of at least 2 units of blood or packed cells
- Symptomatic bleeding in a critical area or organ: intraocular, intracranial, intraspinal, or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding
- A fatal outcome.

Clinically relevant non-major bleedings (CRNM) were defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study treatment, or associated with discomfort for the patient such as pain or impairment of activities of daily life.

All other reported overt bleeding episodes not meeting the criteria for major or clinically relevant non-major bleeding were classified as minimal bleeding. Minimal bleeding events were not be adjudicated.

In the APEX Phase III study there were 25 events of major bleeding in the betrixaban group and 21 events in the enoxaparin group. In the Safety population the rate of major bleeding through seven days after discontinuation of all study medication (primary safety endpoint) was 0.67% in the betrixaban group compared to 0.57% in the enoxaparin group (p = 0.554). One fatal bleeding occurred in each group; (0.03%). The incidence of intracranial haemorrhages through 7 days after discontinuation of all study medication was lower in the betrixaban group (n = 2 [0.05%] vs n = 7 [0.19%]).

The incidence of CRNM bleeds through 7 days after discontinuation of all study medication was higher in the betrixaban group than in the enoxaparin group (**Table 44**).

Table 39. Overview of Adjudicated Bleeding Events through 7 Days after Discontinuation of All Study Medication Safety Population –APEX Study

	Cohort 1		Cohort 2		Overall	
	Betrixaban (N=2,311)	**Enoxaparin** (N=2,310)	**Betrixaban** (N=3,402)	**Enoxaparin** (N=3,387)	**Betrixaban** (N=3,716)	**Enoxaparin** (N=3,716)
Major						
Number of Patients with Events/ Number of Patients At Risk	15/2,311	17/2,310	25/3,402	21/3,387	25/3,716	21/3,716
Event Rate % (95% CI)	0.65 (0.32, 0.98)	0.74 (0.39, 1.08)	0.73 (0.45, 1.02)	0.62 (0.36, 0.88)	0.67 (0.41, 0.94)	0.57 (0.32, 0.81)
CRNM						
Number of Patients with Events/ Number of Patients at Risk	57/2,311	27/2,310	85/3,402	37/3,387	91/3,716	38/3,716
Event rate % (95% CI)	2.47 (1.83, 3.10)	1.17 (0.73, 1.61)	2.50 (1.97, 3.02)	1.09 (0.74, 1.44)	2.45 (1.95, 2.95)	1.02 (0.70, 1.35)
Major or CRNM						
Number of Patients with Events/ Number of Patients at Risk	72/2,311	44/2,310	110/3,402	58/3,387	116/3,716	59/3,716
Event Rate % (95% CI)	3.12 (2.41, 3.82)	1.90 (1.35, 2.46)	3.23 (2.64, 3.83)	1.71 (1.28, 2.15)	3.12 (2.56, 3.68)	1.59 (1.19, 1.99)
Minor						
Number of Patients with Events/ Number of Patients at Risk	72/2,311	31/2,310	99/3,402	47/3,387	104/3,716	51/3,716
Event Rate % (95% CI)	3.12 (2.41, 3.82)	1.34 (0.87, 1.81)	2.91 (2.35, 3.47)	1.39 (0.99, 1.78)	2.80 (2.27, 3.33)	1.37 (1.00, 1.75)
Any Bleeding (Major or CRNM or Minor)						
Number of Patients with Events/ Number of Patients at Risk	144/2,311	75/2,310	209/3,402	105/3,387	220/3,716	110/3,716
Event Rate % (95% CI)	6.23 (5.25, 7.22)	3.25 (2.52, 3.97)	6.14 (5.34, 6.95)	3.10 (2.52, 3.68)	5.92 (5.16, 6.68)	2.96 (2.42, 3.51)

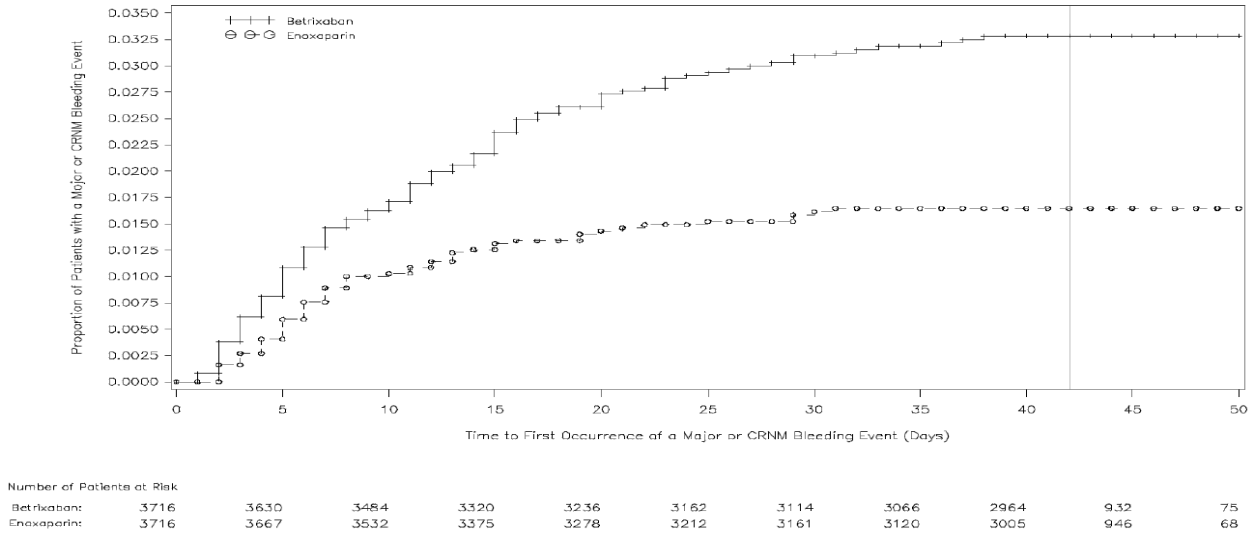
Notes: A patient is counted once for the most severe event if the patient reported more than one event.

The event rate of major or CRNM bleeds was higher in the betrixaban group than in the enoxaparin group ($p = 0.009$, $p < 0.001$, and $p < 0.001$ in Cohort 1, Cohort 2, and overall, respectively).

The adjudicated major bleeding event rate was not significantly increased in the betrixaban group compared with the enoxaparin group in patients who received an actual dose of either 80 or 40 mg betrixaban. In the overall patient population in patients who received the 80 mg dose of betrixaban, an adjudicated major bleeding was reported in 15/2,986 (0.50%) inpatients compared to 16/2,991 (0.53%) in the enoxaparin group.

A Kaplan-Meier plot for adjudicated major or CRNM bleeding events through 7 days after discontinuation of all study medication is provided in **Figure 11** for the overall Safety Population.

Figure 8. Kaplan-Meier Plots for Adjudicated Major or CRNM Bleeding Events through 7 Days after Discontinuation of All Study Medication, Safety Population-APEX Study



A summary of the characteristics of adverse events associated with CRNM bleeding events through seven days after discontinuation of all study medication is presented in **Table 45**.

Table 40. Summary of adverse events associated with CRNM bleeding events through seven days after discontinuation of all study medication - safety population, APEX Study

	Betrixaban (N=91/3716) 2.45%	**Enoxaparin** (N=38/3716) 1.02%	**Total** (N=129/7432)
Adverse Event Severity N (% of total patients with event)			
Mild	38 (41.76)	17 (44.74)	55 (42.64)
Moderate	42 (46.15)	15 (39.47)	55 (44.19)
Severe	11 (12.09)	6 (15.79)	17 (13.18)
Life-Threatening	0	0	0
Adverse Event Seriousness			
Adverse Event	45 (49.45)	20 (52.63)	65 (50.39)
Serious Adverse Event	46 (50.55)	18 (47.37)	64 (49.61)
AE Either Required or Prolonged Hospitalization			
Yes	11 (12.09)	8 (21.05)	19 (14.73)
No	78 (87.91)	30 (78.95)	110 (85.27)
Duration of Adverse Event (days)			
Minimum	1.0	1.0	1.0
Maximum	60.0	72.0	72.0
Median	3.0	2.0	3.0
At Least 3 Days	45 (49.45)	17 (44.74)	62 (48.06)
Unknown Duration	11 (12.09)	2 (5.26)	13 (10.08)

As detailed in the APEX Protocol, all bleeding events were treated according to local standard procedures. If considered to be necessary by the treating physician, the study drug could have been interrupted for up to 7 days. Once bleeding was controlled, the study drug could have been restarted or discontinued according to the treating physician's clinical judgment. A summary of bleeding event management is presented in **Table 46.**

Table 41. Summary of Bleeding Events Management in the APEX study

Patients with Bleeding Events (N)	Major		CRNM		Minor	
	Betrixaban N=25	Enoxparin N=21	Betrixaban N=91	Enoxparin N=38	Betrixaban N=104	Enoxparin N=51
Action Taken with Study Drug						
No Action Taken	5 (20.0)	6 (28.6)	25 (27.5)	11 (28.9)	69 (66.3)	42 (82.4)
Stopped Temporarily	3 (12.0)	0	15 (16.5)	4 (10.5)	20 (19.2)	7 (13.7)
Permanently Discontinued	17 (68.0)	15 (71.4)	51 (56.0)	23 (60.5)	15 (14.4)	2 (3.9)
Treatment Required						
None	3 (12.0)	8 (38.1)	47 (51.6)	20 (52.6)	84 (80.8)	41 (80.4)
Concomitant Medications	5 (20.0)	7 (33.3)	23 (25.3)	7 (18.4)	10 (9.6)	3 (5.9)
Non-Drug Therapies	8 (32.0)	3 (14.3)	14 (15.4)	8 (21.1)	10 (9.6)	5 (9.8)
Concomitant Medications and Non-Drug Therapies	9 (36.0)	3 (14.3)	7 (7.7)	3 (7.9)	0	2 (3.9)

Evaluation of the betrixaban exposure levels measured in bleeding patients (85 in total, including 16 events of major bleeding) provide individual concentrations that cannot provide a clear picture of an increased risk without looking at patients who did not bleed. In that analysis, a statistically significant correlation was observed for higher exposure levels and major or CRNM bleeds (MCRNM bleeds) ($p = 0.017$).

SAEs of hematuria, rectal and upper GI bleeding were reported in a higher number of patients in betrixaban arm, although the incidence was low (0.32, 0.24, and 0.19% of patients, respectively). Serious CRNMs at other anatomical sites were evenly distributed between the treatment arms (**Table 47**).

Table 42. Summary of Adjudicated Serious CRNM Bleeding Events by Anatomical Site - Safety Population

Bleeding Site	Betrixaban (N=3,716) n (%)	Enoxaparin (N=3,716) n (%)	Total (N=7,432) n (%)
Hematuria	12 (0.32)	3 (< 0.1)	15 (0.20)
Rectal	9 (0.24)	2 (< 0.1)	11 (0.15)
Gastrointestinal-Upper (hematemesis or melena)	7 (0.19)	3 (< 0.1)	10 (0.13)
Epistaxis	4 (0.11)	2 (< 0.1)	6 (< 0.1)
Hematoma	4 (0.11)	2 (< 0.1)	6 (< 0.1)
Gastrointestinal-Lower	3 (< 0.1)	2 (< 0.1)	5 (< 0.1)
Other	3 (< 0.1)	2 (< 0.1)	5 (< 0.1)
Hemoptysis	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)
Vaginal (increased or prolonged menstrual our abnormal vaginal bleeding)	2 (< 0.1)	0	2 (< 0.1)
Gingival	0	1 (< 0.1)	1 (< 0.1)
Hemothourax	0	1 (< 0.1)	1 (< 0.1)
Laceration	1 (< 0.1)	0	1 (< 0.1)
Puncture Site	0	1 (< 0.1)	1 (< 0.1)

Of the 45 patients with CRNM bleeding in the betrixaban arm that were designated as SAEs, 11 (24.4%) patients required hospitalisation vs. 8 out of 20 with CRNM bleeding (40.0%) in the enoxaparin arm, who required hospitalisation. In the betrixaban arm 6 events led to new hospitalisation and 5 events prolonged existing hospitalisation. None of the 5 CRNM bleed SAEs met ISTH criteria for major bleeding. All the bleeds resolved, most within 2 to 4 days of onset, with the exception of one upper arm haematoma that resolved within 60 days.

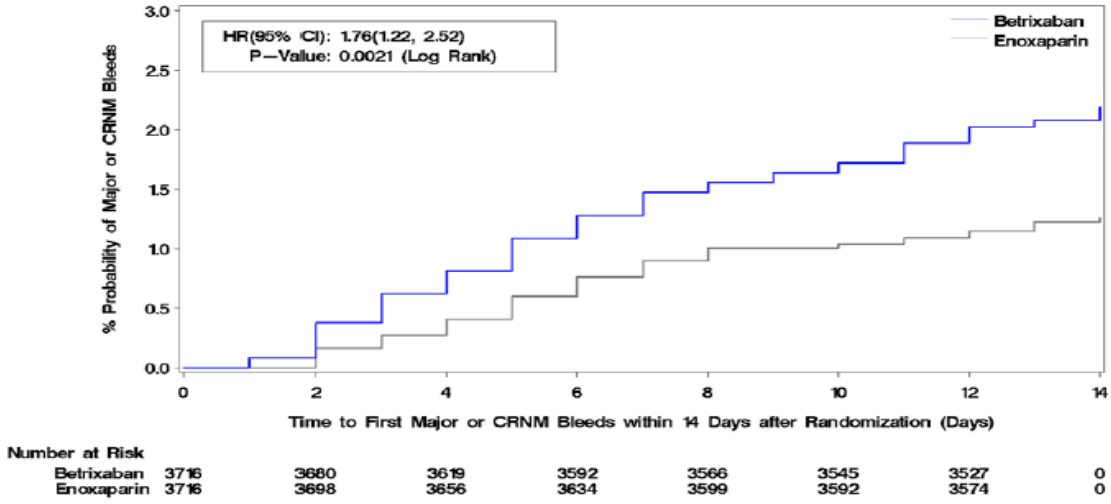
During the procedure, and following the proposed revised indication which excluded patients using the lower 40 mg dose, the applicant provided an updated analysis of the bleeding events in that population (**Table 48**).

Table 43. Rates of Major, CRNM and Major or CRNM Bleeding, 40 mg group

Population	Betrixaban n/N % (95% CI)	Enoxaparin n/N % (95% CI)	Relative Risk (95% CI)[2]	p-Value[3]	ARR (95% CI)[4]
Major Bleeds	10/730 1.37 (0.53, 2.21)	5/725 0.69 (0.09, 1.29)	1.986 (0.682, 5.783)	0.199	-0.68 (-1.72, 0.36)
CRNM Bleeds	25/730 3.42 (2.11, 4.74)	5/725 0.69 (0.09, 1.29)	4.966 (1.912, 12.900)	< 0.001	-2.74 (-4.19, -1.28)
Major or CRNM Bleeds	35/730 4.79 (3.24, 6.34)	10/725 1.38 (0.53, 2.23)	3.476 (1.734, 6.967)	< 0.001	-3.42 (-5.18, -1.65)

Time to event analysis did not show any difference in the 80 mg betrixaban stratum compared to enoxaparin (data not shown), but there was a statistically significant increase in the the probability of major or CRNM bleeding in the betrixaban arm with HR (95% CI) of 1.53 (1.01, 2.31), p = 0.04 (**Figure 12**).

Figure 9. Time to First Major or CRNM bleeding from randomisation to Day 14, Safety Population, 80 mg betrixaban group only



Stroke

Events of strokes reported in the pivotal APEX study are summarised in **Table 49**.

Table 44. Overview of Adjudicated Stroke –APEX Study

	Cohort 1		Cohort 2		Overall	
	Betrixaban (N=2,311)	**Enoxaparin** (N=2,310)	**Betrixaban** (N=3,402)	**Enoxaparin** (N=3,387)	**Betrixaban** (N=3,716)	**Enoxaparin** (N=3,716)
Any Type of Stroke						
Number of Patients with Events/ Number of Patients at Risk	17/2,311	29/2,310	24/3,402	39/3,387	24/3,716	41/3,716
Event Rate % (95% CI)	0.74 (0.39, 1.08)	1.26 (0.80, 1.71)	0.71 (0.42, 0.99)	1.15 (0.79, 1.51)	0.65 (0.39, 0.90)	1.10 (0.77, 1.44)
p-Value	0.075		0.055		0.034	
Ischaemic						
Number of Patients with Events/ Number of Patients at Risk	15/2,311	24/2,310	18/3,402	32/3,387	18/3,716	34/3,716
Event Rate % (95% CI)	0.65 (0.32, 0.98)	1.04 (0.63, 1.45)	0.53 (0.29, 0.77)	0.94 (0.62, 1.27)	0.48 (0.26, 0.71)	0.91 (0.61, 1.22)
p-Value	0.147		0.045		0.026	
Haemorrhagic						
Number of Patients with Events/ Number of Patients at Risk	1/2,311	1/2,310	1/3,402	1/3,387	1/3,716	1/3,716
Event Rate % (95% CI)	0.04 (0.00, 0.13)	0.04 0.00, 0.13)	0.03 (0.00, 0.09)	0.03 (0.00, 0.09)	0.03 (0.00, 0.08)	0.03 (0.00, 0.08)
p-Value	> 0.999		> 0.999		> 0.999	
Uncertain Type						
Number of Patients with Events/ Number of Patients at Risk	0/2,311	1/2,310	1/3,402	1/3,387	1/3,716	1/3,716
Event Rate % (95% CI)	0 (NE, NE)	0.04 (0.00, 0.13)	0.03 (0.00, 0.09)	0.03 (0.00, 0.09)	0.03 (0.00, 0.08)	0.03 (0.00, 0.08)
p-Value	0.500		> 0.999		> 0.999	
Transient Ischaemic Attack						
Number of Patients with Events/ Number of Patients at Risk	1/2,311	3/2,310	4/3,402	5/3,387	4/3,716	5/3,716
Event Rate %(95% CI)	0.04 (0.00, 0.13)	0.13 (0.00, 0.28)	0.12 (0.00, 0.23)	0.15 (0.02, 0.28)	0.11 (0.00, 0.21)	0.13 (0.02, 0.25)
p-Value	0.375		0.753		> 0.999	

Notes: p-Value is based on a 2-sided Pearson Chi-square test. If any expected cell count is less than 5, Fisher exact test is used instead. An ischaemic stroke which occurred prior to a patient's entry into the study and which was considered as a primary risk criteria for study entry was not adjudicated as an ischaemic stroke event.

Serious adverse events

In the APEX study, the total number of patients with SAEs was similar in the betrixaban and enoxaparin groups (657 [18%] and 615 [17%], respectively). This was also true for Cohorts 1 and 2.

The most frequent (occurring in at least 1% of patients) SAEs in the overall betrixaban group were cardiac failure, pneumonia, and chronic obstructive pulmonary disease. The most frequent SAEs in the overall enoxaparin group were cardiac failure, pneumonia, chronic obstructive pulmonary disease, and DVT. Results were similar in Cohorts 1 and 2. The most frequent SAEs in the APEX study were associated with acute medical illnesses which were primary risk criteria/reasons for hospitalisation.

Three SAEs occurred in patients with severe renal impairment who were inadvertently dosed with 80 mg of betrixaban instead of the protocol proscribed reduced 40 mg dose (atrial disease, minor ischaemic stroke considered serious, and decompensated heart failure). None of these SAEs were considered by the investigator to be related to the study drug.

Fatal events

A total of 440 deaths were reported over the course of the clinical development of Betrixaban with three deaths reported in Phase II EXPLORE Xa study and 437 deaths reported in the APEX study. Deaths in betrixaban treated patients (215) were closely matched with active comparators (225) (enoxaparin or warfarin). The three deaths in the EXPLORE Xa study were considered unrelated to study drug.

A total of 437 deaths (213 patients in the betrixaban group, 214 patients in the enoxaparin group, and 10 patients who received no active drug), were recorded in APEX corresponding to mortality rates of 6% in each group.

The CEC adjudicated all deaths occurring up to Day 77. Cause of death was adjudicated for 425 of the 437 patients. Overall, the number of adjudicated deaths was similar in the betrixaban and enoxaparin treatment groups.

The most frequent adjudicated causes of death were: cardiovascular due to heart failure/cardiogenic shock (40 betrixaban patients [19%] vs. 56 enoxaparin patients [26%]); non-cardiovascular due to infection (44 betrixaban patients [21%] vs. 37 enoxaparin patients [17%]); non cardiovascular due to pulmonary causes (28 betrixaban patients [13%] vs. 24 enoxaparin patients [11%]); and other cardiovascular due to ischaemic stroke (including patients who died due to an ischaemic stroke which occurred prior to entry into the study) (24 betrixaban patients [11%] vs. 28 enoxaparin patients [13%]). The incidences of deaths adjudicated as VTE-related were 0.4% in the betrixaban group and 0.7% among the enoxaparin treated patients.

Of the 437 deaths recorded, 418 (206 betrixaban and 212 enoxaparin) were in patients included in the safety analysis of patients who had a treatment emergent fatal AE. The total number of patients with TEAEs leading to death in the overall Safety Population was similar between the two treatments, 206 (5.5%) in the overall betrixaban group versus 212 (5.7%) in the overall enoxaparin group.

The most frequent (occurring in at least 10 patients) TEAEs leading to death in the overall betrixaban group were cardiac failure, respiratory failure, and acute respiratory failure; of these, only respiratory failure and acute respiratory failure were reported more frequently in the overall betrixaban group than in the enoxaparin group. The most frequent TEAEs leading to death in the overall enoxaparin group were cardiac failure, death, pneumonia, ischaemic stroke, and pulmonary embolism.

One death occurred in a patient with severe renal impairment who was inadvertently dosed with 80 mg of betrixaban instead of the protocol specified reduced 40 mg dose. The patient was hospitalised with an acute respiratory failure, had a TEAE of worsening acute respiratory insufficiency that led to his death on Study Day 10; it was considered by the investigator to be unrelated to the study drug. The CEC adjudicated the cause of death as non-cardiovascular due to pulmonary causes.

Other events of interest

- Hypersensitivity

Overall, 1.4% of the patients reported possible hypersensitivity TEAEs, and no difference was seen between the two treatments in the percentages of patients reporting them (1.3% in the betrixaban group vs. 1.4% in the enoxaparin group). The number of patients with serious TEAEs related to hypersensitivity was higher in the enoxaparin group (one patient [< 0.1%] in the betrixaban group vs. eight patients [0.2%] in the enoxaparin group), the numbers were too small to make any clinically meaningful conclusions. No deaths related to hypersensitivity were reported.

- Liver function changes

Betrixaban has not been studied in hepatically impaired patients as they were excluded from clinical studies in the development programme. Betrixaban is primarily excreted in bile, and has no known competitive metabolism through the CYP pathways. Across the development programme in patients with comorbidities and concomitant medications, transient elevations in hepatic enzymes were occasionally reported, but there were no confirmed cases that met all parameters for drug induced liver injury (DILI) or Hy's Law. See further below under Laboratory Findings.

- Acute renal failure

Acute renal failure was reported in 12 versus 11 patients in the betrixaban and enoxaparin groups, respectively (0.3% in each group).

- Neoplasms

History of cancer was one of the additional VTE risk factors included in the APEX study inclusion criteria. History of cancer was balanced between treatment groups with 12.4% of patients in the betrixaban group and by 11.8% of patients in the enoxaparin group. The most frequent malignant neoplasm in both treatment groups was malignant lung neoplasm with 11/3,716 (0.3%) in the betrixaban group and 8/3,716 (0.2%) in the enoxaparin group. All other categories of TEAEs of neoplasms were reported with frequencies below 0.1%.

A total of 50 patients (39 [1.0%] betrixaban and 21 [0.6%] enoxaparin) reported neoplasms that were considered serious; however, only one was considered by the study investigator to be related to the study medication. One patient in the betrixaban group had a non-serious, mild TEAE of adenocarcinoma of the colon diagnosed at SD 7 which was considered possibly related to the study drug by the investigator. The TEAE was unresolved and the study medication was not changed. There were 13 (0.3%) reports of serious neoplasms with a fatal outcome in the Betrixaban group and 8 (0.2%) in the enoxaparin group.

- Irreversible vision loss

There were three reports, one in the Betrixaban group (subconjunctival bleeding).

- Tendon rupture

The musculoskeletal and Connective Tissue and Injury SOCs were searched for potential cases of tendon rupture in APEX. Two enoxaparin patients reported TEAEs of tendonitis and one betrixaban patient reported an SAE of tendon rupture (a severe tendon rupture that was reported as an SAE and considered unrelated to the study drug by the Investigator. The SAE was described as "occasional trauma at home" and the patients recovered without the discontinuation of study medication).

- Idiopathic thrombocytopenia purpura

In APEX there were 27 patients (9 betrixaban and 18 enoxaparin) with TEAEs of thrombocytopenia; the TEAEs were considered serious in two patients. These two patients are described briefly below.

One patient in the betrixaban group had an SAE of severe thrombocytopenia considered possibly related to the study drug by the investigator. The TEAE started on study Day 5. The SAE resolved with the discontinuation of study medication.

One patient in the enoxaparin group had an SAE of moderate thrombocytopenia considered unrelated to the study drug by the investigator. The SAE resolved and study medication was not withdrawn.

Laboratory findings

In the APEX study the two treatment groups were balanced at baseline with regards to haematology parameters, serum chemistry parameters and urinalysis results.

Reported laboratory abnormalities during the APEX study are summarised in **Table 50**.

Table 45. Laboratory abnormalities recorded as treatment emergent adverse events under the investigations system organ class occurring in more than one patient in the Betrixaban group – safety population – APEX Study

System Organ Class/ Preferred Term	**Betrixaban** (N=3,716) **n** (%)	**Enoxaparin** (N=3,716) **n** (%)
INVESTIGATIONS	135 (3.6)	140 (3.8)
Alanine Aminotransferase Increased	15 (0.4)	22 (0.6)
Haemoglobin Decreased	13 (0.3)	10 (0.3)
Creatinine Renal Clearance Decreased	10 (0.3)	14 (0.4)
Hepatic Enzyme Increased	9 (0.2)	13 (0.3)
Aspartate Aminotransferase Increased	8 (0.2)	12 (0.3)
Liver Function Test Abnormal	7 (0.2)	6 (0.2)
Blood Creatine Phosphokinase Increased	5 (0.1)	14 (0.4)
Blood Creatinine Increased	4 (0.1)	5 (0.1)
C-Reactive Protein Increased	4 (0.1)	4 (0.1)
Transaminases Increased	4 (0.1)	4 (0.1)
Blood Potassium Decreased	4 (0.1)	2 (< 0.1)
Blood Magnesium Decreased	4 (0.1)	0
Blood Potassium Increased	3 (< 0.1)	6 (0.2)
Blood Bilirubin Increased	3 (< 0.1)	3 (< 0.1)
International Normalised Ratio Increased	3 (< 0.1)	2 (< 0.1)
Red Blood Cell Count Decreased	3 (< 0.1)	0
Blood Urea Increased	2 (< 0.1)	5 (0.1)
White Blood Cell Count Increased	2 (< 0.1)	2 (< 0.1)
Blood Glucose Increased	2 (< 0.1)	1 (< 0.1)
Activated Partial Thromboplastin Time Prolonged	2 (< 0.1)	0
Blood Phosphorus Decreased	2 (< 0.1)	0
Haematocrit Decreased	2 (< 0.1)	0
Prostatic Specific Antigen Increased	2 (< 0.1)	0

Treatment Emergent Adverse Events Related to Liver Function

A total of 110 liver-related adverse events were reported in the Investigations SOC: 47 in the betrixaban group and 63 in the enoxaparin group. Serious liver-related events in the Investigations

SOC were reported in four patients in the betrixaban group and six patients in enoxaparin group; all liver-related SAEs in the betrixaban group had an outcome of recovered/resolved or recovered/resolved with sequelae.

Liver-related TEAEs were also reported in the Hepatobiliary Disorders SOC. Hepatobiliary disorders occurred in 2.2% of patients in the Safety Population and were evenly distributed between the treatment groups (2.5% in betrixaban treatment group and 1.9% in enoxaparin treatment group).

Evaluation of Potential Drug-Induced Liver Injury

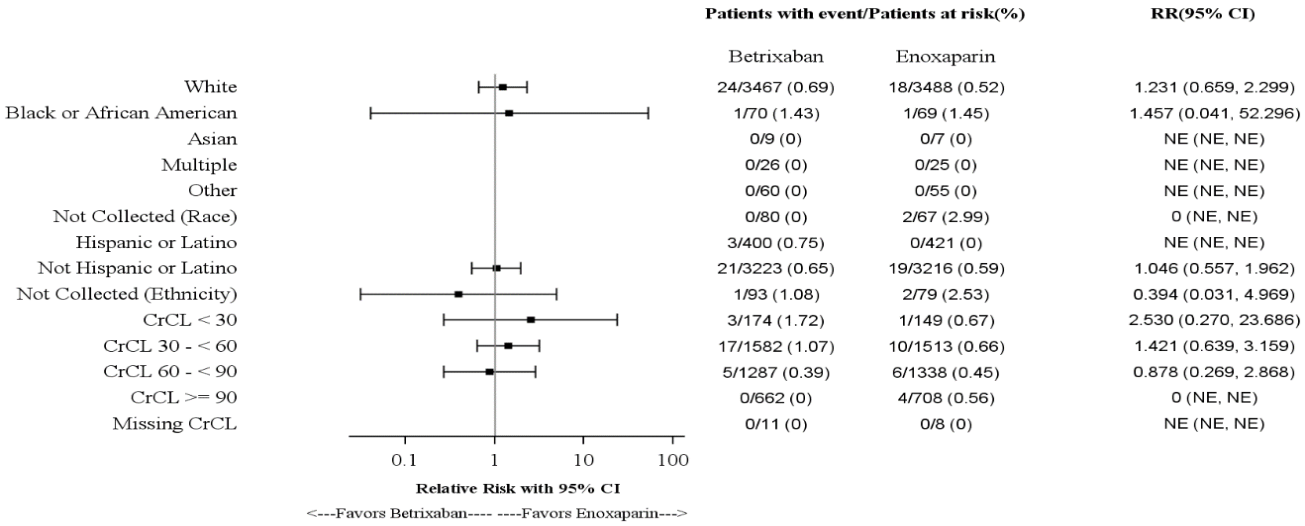
Eight (five betrixaban and three enoxaparin) patients meeting the criteria were identified. Of these eight patients, six (four betrixaban and two enoxaparin) had ALT or AST > 3 x ULN and Bilirubin > 2 x ULN and ALP < 2 x ULN on the same day. Each of the eight patients was evaluated by experts who were blinded to the treatment assignment. There were no confirmed cases of betrixaban induced liver injury in the patients reviewed. Alternative explanations, underlying disease, or other known liver injury causing concomitant medication, were provided in all betrixaban cases.

Safety in special populations

The overall occurrence of adverse events was balanced between the treatment arms and was similar in the age groups < 65 years, 65 to 74 years, and 75 to 84 years (53.0, 53.1, and 53.0%, respectively, in the betrixaban arm vs. 53.4, 51.4, and 49.7%, respectively, in the enoxaparin arm). However, a slightly higher incidence of adverse events was observed in patients who were ≥ 85 years old compared to the other age groups in both study arms (58.6% in the betrixaban arm and 59.7% in the enoxaparin arm). Patients who were 85 years of age and older had a higher frequency of SAEs and adverse events leading to drug withdrawal. The frequency of psychiatric disorders and infections and infestations was also higher in this group of patients.

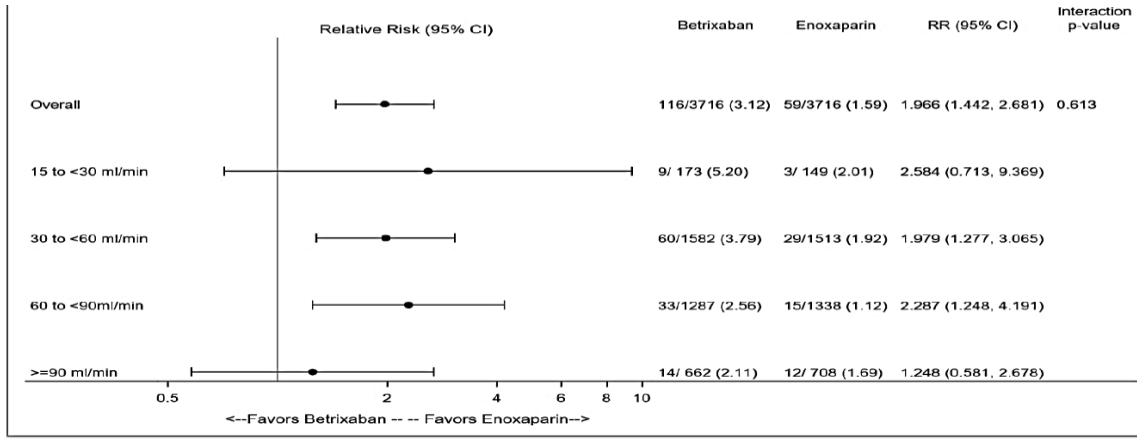
There was a suggestion of an increased risk of major bleeding with decreasing creatinine clearance n patients treated with betrixaban, compared with patients treated with Enoxaparin. There was no increase in adjudicated major bleeding in patients with severe renal insufficiency (3/174 [1.72%] in the Betrixaban group vs. 1/149 [0.67%] in the Enoxaparin group, p = 0.627). Otherwise, there were no remarkable trends in relation to other demographic characteristics (**Figure 13**).

Figure 10. Adjudicated major bleeding through 7 days after discontinuation of all study medication by race, ethnicity, creatinine clearance – APEX Study



Forest plots for the incidence of combined major and CRNM bleedings by creatinine clearance were also presented (**Figure 14**, for the overall safety population).

Figure 11. Major or CRNM Bleeding by Creatinine Clearance— Safety Population, APEX study



NE = Not evaluable; RR = Relative risk
Notes: Creatinine clearance levels were calculated using the Cockcroft and Gault equation at baseline.
Interaction p-value is represented by the Breslow-Day Test of Homogeneity.

Safety related to drug-drug interactions and other interactions

A dedicated drug-drug interaction study (PN010) showed an approximately 3-fold increase in the betrixaban AUC when verapamil was co-administered. In another dedicated drug-drug interaction study (07-009), the co-administration of ketoconazole resulted in a 2-fold increase in the betrixaban AUC. A third study (08-014) compared the PK of betrixaban and digoxin, both substrates but not inhibitors of P-gp. Neither betrixaban nor digoxin had PK levels that were altered in the presence of the other drug, demonstrating that betrixaban concentrations were only likely to be altered in the presence of strong P-gp inhibitors. One additional study evaluated the effect of co-administered proton pump inhibitors as well as antacids on Betrixaban PK (07-008). Neither of these agents had an effect on Betrixaban PK.

Based on these results, future studies reduced the betrixaban dose by 50% in subjects taking strong P-gp inhibitors.

The APEX study identified only two strong P-gp inhibitors that definitively need to be co-administered with a reduced 40 mg dose of Betrixaban: amiodarone and clarithromycin.

Discontinuation due to adverse events

In the Phase III APEX study approximately 382 (10.3%) of patients in the betrixaban group patients discontinued study drug due to compared to 9.7% in the enoxaparin group. The most frequent (occurring in at least 10 patients) TEAEs leading to treatment discontinuation in the overall betrixaban group were atrial fibrillation, haematuria, gastrointestinal haemorrhage, rectal haemorrhage, epistaxis, and ischaemic stroke; all of these TEAEs leading to treatment discontinuation were reported by more patients in the overall betrixaban group than in the enoxaparin group with the exception of atrial fibrillation.

Among TEAEs leading to treatment discontinuation sepsis was reported with a higher incidence in the betrixaban treatment arm as compared to the enoxaparin arm (7 vs. 0 events).

2.6.1. Discussion on clinical safety

The majority of the 7,513 patients included in the phase III, pivotal study APEX had been hospitalised for decompensated heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke and were also immobilised/had reduced mobility.

The two treatment arms in the trial were balanced for baseline criteria. The concomitant diseases and co-medications reflected this elderly and frail group of patients. Most common co-morbidities in the study population were hypertension, cardiac failure, chronic obstructive pulmonary disease, myocardial ischemia, and chronic cardiac failure.

Even though the treatment period was longer for betrixaban than for enoxaparin, patients in both groups had the same period of follow-up.

No individual TEAE was reported in more than 4% of patients in either group, and treatment group differences were generally small (<2% difference). Results were generally similar in the overall Safety Population and in Cohorts 1 and 2. The most frequent TEAEs (reported in more than 100 patients) in the overall betrixaban group were cardiac failure, urinary tract infection, and constipation; all of these TEAEs were reported by a greater percentage of patients in the overall betrixaban group than in the overall enoxaparin group, although the differences between groups were small. The most frequent TEAEs in the overall enoxaparin group were atrial fibrillation and constipation.

The main safety issue identified, as expected by the mechanism of action of betrixaban was bleeding.

Events of major bleeding were balanced between patients treated with betrixaban and enoxaparin, (25 and 21 patients respectively), whereas CRNM bleeding was more frequent in the betrixaban group (91 compared to 38 in patients on enoxaparin, p< 0,001).

The ISTH criteria for major bleedings are rather restrictive resulting in low numbers of events which make comparisons between treatment groups uninformative. Therefore the overall bleeding rates are important to take into account in order to assess the risk of bleeding in association with a specific anticoagulant regimen.

The distribution of bleeding sites was as expected for a Xa inhibitor with a rather large fraction related to mucosal bleedings.

There was one fatal bleeding in each of the betrixaban group and the enoxaparin group. Intracranial haemorrhage was reported in 2 betrixaban patients and in 8 enoxaparin patients (including the fatal event in this treatment arm). All intracranial haemorrhages except one occurred in the window through 7 days after discontinuation of all study medication, which was used for the analysis of the primary safety endpoint. The numbers of intracranial bleeding are low precluding any definite conclusions on potential differences on the level of risk for this type of events between the two treatments.

The incidence of CRNM bleeds through 7 days after discontinuation of all study medication was higher in the betrixaban group than in the enoxaparin group which possibly could be due to the longer duration of exposure to betrixaban than to enoxaparin. The incidences of bleedings leading to treatment interruption were 3.8% and 1.9% in the betrixaban and enoxaparin groups, respectively.

The higher incidence of clinically relevant bleedings in the betrixaban arm is of concern. The number of patients requiring prolonged hospitalization or readmission did not differ substantially between the two treatment groups which to some extent is reassuring. On the other hand the number of patients experiencing a bleeding event of more than 3 days' duration was much higher in the betrixaban treatment arm (28 vs. 12 events). The rather slow elimination rate of betrixaban and the current lack of effective reversal agents are aspects that need to be taken into account in relation to such observations, as they make these events more difficult to manage. This is illustrated by the fact that for the combined outcome of major and CRNM bleeding, the incidences of bleedings requiring blood transfusions, surgical/medical consultation/intervention and hospitalization were approximately doubled in the betrixaban group compared to enoxaparin. The incidences of bleedings leading to treatment interruption were also higher (3.8% and 1.9%) in the betrixaban compared to enoxaparin.

Importantly, the observed difference in the level of risk was not driven by the difference in the period on treatment between the betrixaban and enoxaparin groups. Time to event analysis showed a clear difference between the two groups in the first 14 days following randomisation. This was apparent for both the overall safety population but also the 80 mg stratum of the betrixaban patients which the applicant considered to be at a lower risk for this type of events. These results demonstrate that betrixaban has a higher risk for bleeding compared to enoxaparin.

The applicant provided betrixaban plasma concentrations for 85 patients who had experienced a bleeding event. This included 16 major bleedings and 69 CRNM bleedings. There was a statistical significant correlation between higher exposure of betrixaban and the occurrence of bleeding. A detailed analysis of these events revealed however that several events occurred with betrixaban concentration below 10 ng/ml. In addition, there were a lot of patients with a high concentration of betrixaban (higher than 60 mg/ml) who did not experience a bleeding event.

In all three populations, the betrixaban group experienced a lower number of any type of stroke, with the difference between groups clearest in the overall Safety Population. This difference was primarily driven by ischaemic strokes. The ischaemic stroke event rate was 18/3,716 (0.48%) in the betrixaban treatment group vs. 34/3,716 (0.91%) in the Enoxaparin treatment group ($p = 0.026$). One haemorrhagic stroke occurred in each group. Prevalence of a history of atrial fibrillation was more common in the enoxaparin group (as was the incidence of AF during the trial, as compared to the betrixaban treated patients), which could possibly provide an explanation for this observation.

For patients with severe renal impairment, the dose was reduced to 40 mg according to the protocol of the APEX study. The applicant considered that the patients who received the adjusted 40 mg dose (approximately 20% of mITT patients in each treatment arm) did not achieve the targeted exposure to

betrixaban and had substantially decreased efficacy compared to patients receiving the 80 mg dose. While there was no benefit of the use of betrixaban in terms of prevention on VTE events, there was an increase in both major (RR 2.53 95% CI 0.27-23.69) and the composite of major and CRNM bleeding (even if non-statistically significant) with betrixaban (5.47%) as compared to enoxaparin (0.93%).

There was a suggestion of an increased risk of major bleeding with decreasing creatinine clearance in patients treated with betrixaban, compared with patients treated with enoxaparin, although the 95% CIs for the event rates in all of the creatinine clearance categories overlapped. For the combination of major and CRNM bleedings interaction test for the relative risk of bleeding comparing betrixaban to enoxaparin across the CrCl subgroups was not significant, however the relative risk of bleeding was strongly increased with betrixaban. In each CrCl subgroup, there were twice more bleeding events with betrixaban than with enoxaparin. It is acknowledged that the treatment duration was longer with betrixaban than with enoxaparin and thus can explain part of this increase.

Causality between liver AEs and study drug is not clear, and there are no confirmed cases with drug induced liver injury. Use of betrixaban was proposed to be contraindicated for patients with hepatic impairment.

Women had more bleeding events in the betrixaban group compared to the enoxaparin group (0,94% vs. 0,40%), but the number of events were low. When looking at all bleeding events, including CRNM, there were no differences between sexes.

Older patients had numerically higher number of bleeding events with betrixaban, but the difference was not significant.

Frequency of neoplasms was low in both treatment groups. Although the observation period was short, there is no suggestion of any causality between betrixaban and neoplasms.

The two strong P-gp inhibitors that had been previously evaluated in the Phase I study, verapamil and ketoconazole, increased betrixaban concentrations but not to the same degree as was observed in the dedicated DDI studies, possibly because those studies had been conducted under fasting condition and the medications had been administered simultaneously. To minimise these risks it was proposed to contraindicate the use of betrixaban with concomitant use of potent P-gp inducers and inhibitors. Furthermore, as taking betrixaban on an empty stomach could lead to an approximate doubling of the dose compared with that when administered with food, betrixaban should always be taken with food.

Additional expert consultations

See discussion on clinical efficacy.

2.6.2. Conclusions on the clinical safety

The major identified safety concern associated with betrixaban use was an increased risk of bleedings. Even though no difference was observed in terms of major bleedings between betrixaban and enoxaparin, there was a significant difference in the clinically relevant non major bleedings. This difference for a product intended for use in an elderly, fragile population, may have important clinical consequences even if not classified as major bleedings according to the conservative ISTH criteria. Importantly, the difference in these events is not due to the extended period of anti-coagulation for betrixaban, but is higher in the head to head comparison of the two treatments.

In addition, the long-half life and the significant food effect on betrixaban exposure combined with the patient characteristics of the intended target population make these events more difficult to predict and manage effectively.

2.7. Risk Management Plan

Safety concerns

Type of risk	Risk
Important identified risks	Haemorrhage and off-label use in patients with bleeding comorbidities
Important potential risks	Renal toxicity Drug-drug interaction with CYP-3A4 substrates
Missing information	Use in patients who are in need of urgent surgery Use in patients who need prolonged anticoagulation Use in patients with active cancer Off-label use in conditions indicated for other FXa inhibitors, e.g., use in Patients with Prosthetic Heart Valves Potential off-label use in patients who are pregnant due to increased risk of maternal bleeding seen preclinically in animals. Potential for hepatotoxic effects when used in patients with mild or moderate hepatobiliary disorders.

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Submit date: interim or final reports (planned or actual)
PASS: A Cross-Sectional Epidemiological PASS to Measure Physician and Patient Awareness and Understanding of the Key Messages in the Prescriber Guide and Patient Card and Characterise Patient and Physician Knowledge of Key Safety Messages	Evaluate the effectiveness of the risk minimisation activities (Patient Alert Card and Prescriber's Guide) by: 1) Investigate whether physicians have received the educational materials. Assess knowledge and understanding among physicians regarding key safety information contained in the prescriber guide.	Haemorrhage, and off-label use in patients with bleeding comorbidities	Interim reports planned to be submitted with each PSUR until the quota of patient numbers is reached Planned final report: 30 Sep 2021

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Submit date: interim or final reports (planned or actual)
Following Administration of Dexxience Category 3	2) Characterise the HCP's understanding of the suitability of patients selected for treatment with Dexxience with regard to the published dosing recommendations, contraindications and warning and precautions. 3) Assess knowledge and understanding of patients regarding the key safety information contained in the patient card and determine if the patients use and carry the patient card with them. 4) Observing and measuring patient understanding of dosing regimen, and life-style modifications to minimise the risk of injury		
Clinical Study: A safety and efficacy study to assess the use of Dexxience in patients with hepatic impairment, Category 3	**Primary Objective:** To determine the effect of mild and moderate hepatic impairment on the pharmacokinetic (PK) properties of a single dose of Dexxience. **Secondary Objectives:** To evaluate the overall safety of Dexxience in patients with mild to moderate hepatic impairment. To determine the effect of mild and moderate hepatic impairment on the pharmacodynamic (PD) properties of a single dose of Dexxience.	Missing information for use in patients with hepatic impairment	Final Report planned 30 Jun 2019
DUS: A pharmaco-epidemiological study	To provide a detailed description of patients who are prescribed	Provide real-world data	Interim reports planned to be

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Submit date: interim or final reports (planned or actual)
of Dexxience use in routine clinical practice in the United Kingdom Category 3	oral Dexxience for the first time and describe the characteristics of Dexxience use (including specific AMI, presence of contraindications and duration of treatment).	related to the post approval prescription patterns of Dexxience.	submitted with each PSUR until the quota of patient numbers is reached Planned final report: 30 Sep 2021
Drug–Drug interaction Study in CYP3A4 Substrates Category 3	A clinical study to evaluate the potential for 3A4 induction by Dexxience using the 3A4 substrate, midazolam, which has been shown to be a sensitive marker for detecting 3A4 inhibition or induction by a suspected compound. Midazolam exposure before and after Dexxience co-administration will be compared using commonly accepted statistical methods. A 7-day course of Dexxience, including the loading dose on the first day, is expected to result in plasma concentrations at or near steady-state and be sufficient to evaluate any clinically significant 3A4 induction by Dexxience.	Potential concern: Drug-Drug Interaction with CYP3A4 Substrates	The study can be conducted and completed within one year of MAA approval. Planned final report: 30 Apr 2019

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Haemorrhage and off-label use in patients with bleeding comorbiditie	The safety concern is adequately addressed in SmPC: **Section 4.4 of SmPC (Special warnings and precautions for use)** states: "Haemorrhage risk Betrixaban increases the risk of bleeding and can cause serious, potentially fatal bleeding. Betrixaban is	Prescriber's Guide: To ensure that treating physicians are made aware of the risk of bleeding associated with Dexxience administration, and the contraindications that are in

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
s	recommended to be used with caution in conditions with increased risk of bleeding. Patients should be advised of signs and symptoms of blood loss and instructed to report them immediately and seek emergency care. Any signs or symptoms of blood loss should be promptly evaluated and the need for blood replacement be considered. Discontinue betrixaban in patients with active pathological bleeding (see sections 4.8 and 4.9). Management of bleeding: Should a serious bleeding complication arise in a patient receiving betrixaban, the next betrixaban administration should be delayed or treatment should be discontinued as appropriate. Management of bleeding events should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g., for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets. There is no established way to reverse the anticoagulant effect of betrixaban, which can be expected to persist for at least 72 hours after the last dose. Protamine sulphate, vitamin K, and tranexamic acid are not expected to reverse the anticoagulant activity of betrixaban. The anticoagulant effect of betrixaban cannot be reliably monitored with standard laboratory testing. A specific anticoagulant reversal agent for betrixaban is not available. Haemodialysis is not expected to significantly contribute to betrixaban clearance. **Section 4.3 of the SmPC lists the following as contraindications:** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Active clinically significant bleeding. Severe hepatic impairment or hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration; presence of malignant neoplasms at high risk of bleeding; recent brain or spinal injury; recent brain, spinal or ophthalmic surgery; recent	place, in order to minimise the Dexxience use in patients with bleeding comorbidities. A Prescriber's Guide will be distributed to all major pharmacies and associated hospitals, and delivered to each Physician seen by a Portola Medical Representative. The Prescriber's Guide will reinforce key safety information from the SmPC, to help support appropriate prescribing behaviour. The Prescriber's Guide will alert the Physician to the risk of bleeding with Dexxience use, and highlight the lack of an antidote. The Prescriber's Guide also reinforces the importance of careful review of the SmPC, and full explanation of the Patient Alert Card to the patient prior to use of the product. Patient Alert Card: To ensure that patients are made aware of the risk of bleeding associated with Dexxience administration, and the contraindications that are in place, in order to minimise the Dexxience use in patients with bleeding comorbidities, and to maximise patient compliance with the dosing regimen, and to modify behaviours which minimises the likelihood of accidents. A Patient Alert Card will be

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	intracranial haemorrhage; known or suspected oesophageal varices; arteriovenous malformations; vascular aneurysms; or major intraspinal or intracerebral vascular abnormalities. Concomitant treatment with any other anticoagulants, e.g., unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, rivaroxaban, apixaban, etc.). Co-administration of betrixaban with medicinal products that are potent P-glycoprotein (P-gp) inducers (e.g., rifampicin, rifabutin, St. John's wort [*Hypericum perforatum*], carbamazepine, phenobarbital and phenytoin) is contraindicated. Co-administration will significantly decrease betrixaban plasma concentrations and could result in loss of efficacy (see section 4.5). Co-administration of betrixaban with medicinal products that are potent P-gp inhibitors (e.g., amiodarone, verapamil, clarithromycin, ritonavir, itraconazole, azithromycin, quinidine) is contraindicated. Co-administration will significantly increase betrixaban plasma concentrations and could result in significant risk for bleeding (see section 4.5). **Section 2 of the PIL (What you need to know before you take Dexxience)** states: **Do not take Dexxience:** if you are allergic to betrixaban or any of the ingredients of this medicine (listed in section 6) if you are actively bleeding if you have a severe liver disease or liver disease which leads to increased risk of bleeding (hepatic coagulopathy) if you have severely reduced kidney function if you have a disease or condition that increases the risk of serious bleeding (such as an active or recent ulcer of your stomach or bowel, injury or bleeding in the brain or spine, recent surgery of the brain, spine or eyes, enlarged veins in the oesophagus, or malformations or abnormal widening of a vein or artery) if you are taking other medicines to prevent blood clotting (e.g., warfarin, dabigatran, rivaroxaban,	included within the Dexxience packaging, and will therefore be delivered to each patient. The Patient Alert Card will alert the Patient to the risk of bleeding with Dexxience use, and provide advice on how to minimise the risks and encourage the patient to discuss concomitant medications, medical history, and future surgical plans with the prescriber. It will also advise the patient on what to do in the event of a bleeding episode. The Patient Alert Card will have sections to be completed by the patient with contact details and blood type, as well as other medications they are taking. It will also include a space to enter the treating physician's details to be contacted in case of emergency, and a note to the HCP that there is no antidote.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	apixaban or heparin) if you are taking other medications that may increase the effects of Dexxience and the chance of unwanted bleeding (e.g., amiodarone, verapamil, clarithromycin, ritonavir, itraconazole, quinidine) if you are taking other medicines that may reduce the ability of Dexxience to help prevent blood clots from forming (e.g., rifampicin). **Warnings and precautions** Talk to your doctor or pharmacist before taking Dexxience if you have the following: An increased risk of bleeding, such as: bleeding disorders, including conditions resulting in reduced platelet activity severe liver disease recent bleeding in your brain (intracranial) active cancer a liver problem or a history of liver problems kidney disease if you have a mechanical heart valve If you need to have surgery or a procedure which may cause bleeding, your doctor might ask you to temporarily stop taking this medicine for a short while. If you are not sure whether a procedure may cause bleeding, ask your doctor. No other SmPCs exist for this product as it is not yet approved for marketing use within the EEA. **Other routine risk minimisation measures** None	

Important potential risks		
Renal toxicity	To make prescribers and patients aware that it is not known whether Dexxience may potentially cause renal toxicity. The safety concern is adequately addressed in SMPC: **Section 4.2 of SmPC (Posology - Renal impairment)** states:	None

	"No dose reduction is required in patients with mild or moderate renal impairment, i.e., when creatinine clearance (CrCl) > 30 mL/min. Betrixaban is not recommended in patients with severe renal impairment (CrCl ≥ 15 mL/min to < 30 mL/min) because it is currently not possible to propose an adequate dose in this patient population (see section 4.4)." **Section 5.2 of SmPC (Pharmacokinetic Properties – Elimination)** states: "Betrixaban is excreted mostly unchanged through the bile with low renal excretion; approximately 5% of the administered oral dose is found in the urine unchanged. In a study of intravenous betrixaban a median value of 17.8% of the absorbed dose was observed as unchanged betrixaban in urine. The effective half-life is 19 to 27 hours and the terminal elimination half-life is approximately 38 hours. Following oral administration of betrixaban approximately 85% of the administered compound was recovered in the faeces and 11% recovered in the urine." **Section 5.2 of SmPC (Pharmacokinetic Properties – Special Populations) Renal impairment** states: In patients with severe renal impairment (CrCl greater than 15 and less than 30 mL/min) receiving 80 mg betrixaban the exposure is predicted to be approximately 21% higher than the typical patient with mild to moderate renal impairment. Betrixaban is not recommended in patients with severe renal impairment (CrCl ≥ 15 mL/min to < 30 mL/min) because it is currently not possible to propose an adequate dose in this patient population (see sections 4.2 and 4.4). Comment (e.g., on any differences between SmPCs) No other SmPCs exist for this product as it is not yet approved for marketing use within the EEA. Other routine risk minimisation measures None.	
Drug-drug interaction with CYP3A4 substrates	To make prescribers and patients aware that when co administered with a narrow CYP3A4 substrate, based on *in vitro* results, there is a risk for 3A4 enzyme induction by betrixaban. This may result in reduced efficacy of co-administered medicinal products that are narrow substrates of CYP3A4, collect information and monitor changes to the product risk:benefit profile through routine Pharmacovigilance. Therefore, the SmPC of the co-administered medicinal product should be consulted.	None

	The safety concern is adequately addressed in SmPC: **Section 4.5 of SmPC (Interaction with other medicinal products and other forms of interaction)** states: <u>Cytochrome P450 3A4 (CYP3A4) inhibitors and inducers</u> Betrixaban has limited interaction with CYP enzymes. Less than 1% of the absorbed medicinal product is metabolised by CYP enzymes, and the medicinal product does not inhibit CYP enzymes at typical levels of exposure. The CYP3A4 levels increased slightly at high concentrations, and thus may increase the rate of elimination of drugs that are eliminated by CYP3A4 and reduce their effectiveness. Therefore, the SmPC of the co--administered medicinal product should be consulted. **Section 5.2 of the SmPC Pharmacokinetic Properties - Biotransformation** states: Approximately 7.6% of the administered betrixaban is excreted in urine as parent compound. A similar amount (6%) excreted in the urine is comprised of metabolites. However, most of the administered material excreted in the faeces is intact betrixaban. Betrixaban is primarily metabolised by hydrolysis that is not mediated by any CYP enzymes. Trace levels of the minor metabolites O desmethyl betrixaban and N desmethyl betrixaban are formed via metabolism by several CYP enzymes. **Section 2 of the PIL (Other medicines and Dexxience)** states: Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Your doctor will decide if you should be treated with Betrixaban Portola when taking these medicines. This is because some of these medicines are contraindicated. Tell your doctor or pharmacist if you are taking any of the following: • some medicines for bacterial or fungal infections (e.g., clarithromycin, azithromycin, itraconazole) **Section 3 of the PIL (How to take)** states: Following an initial dose of 160 mg (two 80 mg capsules) on the first day, the recommended dose is one 80 mg capsule once daily. No other SmPCs exist for this product as it is not yet approved for marketing use within the EEA. Other routine risk minimisation measures None	

Important Missing Information		
Use in patients who are in need of urgent surgery	Educate and warn prescribers via the SmPC, PIL; To make prescribers and patients aware that Dexxience has not been studied in this specific subgroup of patients, and provide information to a health care provider to make a specific decision to prescribe Dexxience with prior knowledge of the known and unknown risks. Collect information and monitor changes to the product risk:benefit profile through routine Pharmacovigilance. To make prescribers and patients aware that Dexxience has not been studied in this sub-group of patients, and the recommended duration of treatment of Dexxience is 35 to 42 days. The safety concern is adequately addressed in SmPC: **Section 4.4 of SmPC (Special warnings and precautions for use) Haemorrhage risk** states: Betrixaban increases the risk of bleeding and can cause serious, potentially fatal bleeding. Betrixaban is recommended to be used with caution in conditions with increased risk of bleeding. Patients should be advised of signs and symptoms of blood loss and instructed to report them immediately and seek emergency care. Any signs or symptoms of blood loss should be promptly evaluated and the need for blood replacement be considered. Discontinue betrixaban in patients with active pathological bleeding (see sections 4.8 and 4.9). Management of bleeding: Should a serious bleeding complication arise in a patient receiving betrixaban, the next betrixaban administration should be delayed or treatment should be discontinued as appropriate. Management of bleeding events should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g., for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets. There is no established way to reverse the anticoagulant effect of betrixaban, which can be expected to persist for at least 72 hours after the last dose. Protamine sulphate, vitamin K, and tranexamic acid are not expected to reverse the anticoagulant activity of betrixaban. The anticoagulant effect of betrixaban cannot be reliably monitored with standard laboratory testing. A specific anticoagulant	None

	reversal agent for betrixaban is not available. Haemodialysis is not expected to significantly contribute to betrixaban clearance. The anticoagulant effect of betrixaban cannot be reliably monitored with standard laboratory testing. Although treatment with betrixaban does not require routine monitoring of exposure, betrixaban levels measured with a calibrated quantitative anti-FXa assay could be useful in exceptional situations where knowledge of betrixaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery. **Section 4.4 of SmPC (Special warnings and precautions for use)** **Discontinuation for surgery and other interventions** states: Dexxience should be discontinued at least 72 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding. This includes interventions for which the probability of clinically significant bleeding cannot be excluded or for which the risk of bleeding would be unacceptable. If surgery or invasive procedures cannot be delayed, appropriate caution should be exercised, taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention. **Section 2 of the PIL (Warnings and precautions)** states: Talk to your doctor or pharmacist before taking Dexxience. If you need to have surgery or a procedure which may cause bleeding, your doctor might ask you to temporarily stop taking this medicine for a short while. If you are not sure whether a procedure may cause bleeding ask your doctor. Comment (e.g., on any differences between SmPCs) No other SmPCs exist for this product as it is not yet approved for marketing use within the EEA. Other routine risk minimisation measures None	
Use in patients who need prolonged anticoagulation	Educate and warn prescribers via the SmPC, PIL; To make prescribers and patients aware that Dexxience has not been studied in this specific subgroup of patients, and provide information to a health care provider to make a specific decision to prescribe Dexxience with prior knowledge of the known and unknown risks and that the	None

	recommended duration of treatment of Dexxience is 35 to 42 days. Collect information and monitor changes to the product risk:benefit profile through routine Pharmacovigilance. The safety concern is adequately addressed in SmPC: **Section 4.1 of SmPC (Therapeutic indications)** states: Prophylaxis of venous thromboembolism (VTE) in adults hospitalised for an acute medical illness (such as acute heart failure, respiratory insufficiency, severe infections, acute rheumatic diseases, or ischemic stroke) who are at risk for thromboembolic complications due to restricted mobility and other risk factors for VTE (see section 5.1). **Section 4.2 of SmPC (Posology and method of administration)** states: The recommended dose is 160 mg betrixaban on Day 1, followed by 80 mg taken once daily for 35 to 42 days, taken with food preferably at the same time each day. Due to the risk of increased exposure, betrixaban should not be taken without food (see section 5.2). Switching treatment from parenteral anticoagulants to betrixaban (and vice versa) can be done at the next scheduled dose. These medicinal products should not be administered simultaneously (see section 4.5). If a patient develops a thrombosis while taking betrixaban, thromboprophylaxis with betrixaban should be stopped and treatment should be initiated per local clinical guidelines. Following an individual assessment in which the timing of the last dose of betrixaban is taken into consideration, therapeutic anticoagulation should be initiated. Comment (e.g., on any differences between SmPCs) No other SmPCs exist for this product as it is not yet approved for marketing use within the EEA. Other routine risk minimisation measures None	
Use in patients who have active cancer	Educate and warn prescribers via the SmPC, PIL; To make prescribers and patients aware that Dexxience has not been studied in this specific subgroup of patients, and provide information to a health care provider to make a specific decision to prescribe Dexxience with prior knowledge of the known and unknown risks. Collect information and monitor changes to the product risk:benefit profile through routine Pharmacovigilance. The safety concern is adequately addressed in SmPC:	None

	Section 4.4 in SmPC (Special warnings and precautions for use) states: Patients with active cancer Efficacy and safety of betrixaban in the prevention of VTE in patients with active cancer have not been established. **Section 2 of the PIL (Warnings and precautions)** states: Talk to your doctor or pharmacist before taking Dexxience if you have the following: Active cancer Comment (e.g., on any differences between SmPCs) No other SmPCs exist for this product as it is not yet approved for marketing use within the EEA. Other routine risk minimisation measures None	
Off-label use in patients with conditions indicated for other FXa inhibitors e.g., use in patients with Prosthetic Heart Valves	Educate and warn prescribers via the SmPC, PIL; To make prescribers and patients aware of the correct indications for use and to make prescribers and patients aware that Dexxience has not been studied in this specific subgroup of patients, and provide information to a health care provider to make a specific decision to prescribe Dexxience with prior knowledge of the known and unknown risks. Collect information and monitor changes to the product risk:benefit profile through routine Pharmacovigilance. The safety concern is adequately addressed in SmPC: **Section 4.1 of SmPC (Therapeutic indications)** states: Prophylaxis of venous thromboembolism (VTE) in adults hospitalised for an acute medical illness (such as acute heart failure, respiratory insufficiency, severe infections, acute rheumatic diseases, or ischemic stroke) who are at risk for thromboembolic complications due to restricted mobility and other risk factors for VTE (see Section 5.1). **Section 4.4 of the SmPC (Special Warnings and Precautions)** states: Patients with prosthetic heart valves The safety and efficacy of betrixaban have not been studied in patients with prosthetic heart valves. Therefore, use of betrixaban is not recommended in these patients. **Section 1 of the PIL (What Dexxience is and what it is used for)** states: Dexxience contains the active substance betrixaban and belongs to a group of medicines called anticoagulants. This medicine helps to prevent blood clots from forming. It	None

	works by blocking the activity of FXa, which is an important component of blood clotting. For Prosthetic Heart Valves specifically: The safety concern is adequately addressed in SmPC. **Section 2 of the PIL (Warnings and precautions)** states: Talk to your doctor or pharmacist before taking Dexxience if you have a mechanical heart valve. No other SmPCs exist for this product as it is not yet approved for marketing use within the EEA Other routine risk minimisation measures None	
Use in patients who are pregnant as there is an increased risk of bleeding as seen preclinically in animals	Educate and warn prescribers via the SmPC, PIL; To make prescribers and patients aware that Dexxience has not been studied in pregnant patients, and provide information to a health care provider to make a specific decision to prescribe Dexxience with prior knowledge of the known and unknown risks. Collect information and monitor changes to the product risk:benefit profile through routine Pharmacovigilance. To make prescribers and patients aware of the increase risk of bleeding when Dexxience is administered during pregnancy. The safety concern is adequately addressed in SmPC: **Section 4.6 of SmPC (Fertility, pregnancy, and lactation)** states: There are no data from the use of Dexxience in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Although Dexxience was not associated with adverse developmental foetal outcomes in animals, maternal toxicity (i.e., haemorrhage) was identified in these studies. Dexxience is not recommended during pregnancy. Treatment with Dexxience is likely to increase the risk of haemorrhage during pregnancy and delivery. Dexxience should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and foetus. Consider the risks of bleeding and of stroke in using Dexxience in this setting. **Section 2 of the PIL (Pregnancy and breast-feeding)** states: Dexxience is not recommended if you are pregnant. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Taking	None

	this medicine while pregnant may increase the risk of bleeding. No other SmPCs exist for this product as it is not yet approved for marketing use within the EEA. Other routine risk minimisation measures None	
Potential for hepatotoxic effects when used in patients with mild or moderate hepatobiliary disorders.	Educate and warn prescribers via the SmPC, PIL; To make prescribers and patients aware that Dexxience has not been studied in patients with mild or moderate hepatic impairment, and provide information to a health care provider to make a specific decision to prescribe Dexxience with prior knowledge of the known and unknown risks. Collect information and monitor changes to the product risk:benefit profile through routine Pharmacovigilance. The safety concern is adequately addressed in SmPC: **Section 4.2 of SmPC (Posology and Administration)** states: Hepatic impairment Betrixaban is contraindicated in patients with severe hepatic impairment or hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see Section 4.3). Use of betrixaban is not recommended in patients with mild or moderate hepatic impairment (see sections 4.4 and 5.2). **Section 4.3 of SmPC (Contraindications)** states: Severe hepatic impairment or hepatic disease associated with coagulopathy and clinically relevant bleeding risk. **Section 4.4 of SmPC (Special warnings and precautions for use - Hepatic impairment)** states: Dexxience is contraindicated in patients with severe hepatic impairment or hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Efficacy and safety of betrixaban in patients with hepatic impairment has not been studied. Therefore, use of betrixaban is not recommended in patients with mild, moderate hepatic impairment (see sections 4.2 and 5.2). **Section 5.2 of SmPC (Pharmacokinetic properties - Hepatic impairment)** states: Hepatic impairment Studies with betrixaban in patients with hepatic impairment have not been conducted and the impact of hepatic impairment on the exposure to betrixaban has not	None

	been evaluated. Since hepatic impairment is expected to increase betrixaban exposure, the use of Dexxience in patients with any hepatic impairment or with any hepatic disease associated with coagulopathy should be avoided (see sections 4.2 and 4.3). **Section 2 of the PIL (What you need to know before you take Dexxience)** states: **Do not take Dexxience:** if you have a severe liver disease or liver disease which leads to increased risk of bleeding (hepatic coagulopathy) **Warnings and precautions** Talk to your doctor or pharmacist before taking Dexxience if you have the following: severe liver disease, liver problem or a history of liver problems No other SmPCs exist for this product as it is not yet approved for marketing use within the EEA. Other routine risk minimisation measures None	

Conclusion

The CHMP and PRAC, having considered the data submitted in the application, were of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

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.

Periodic Safety Update Reports submission requirements

Not applicable.

2.9. New active substance

The applicant compared the structure of betrixaban with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers betrixaban to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union. However, in light of the negative recommendation, the new active substance status is not applicable at this stage.

2.10. Product information

In light of the negative recommendation, a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

2.10.1. 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*. However, in light of the negative recommendation, a satisfactory package leaflet cannot be agreed at this stage.

2.10.2. Additional monitoring

Not applicable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Patients hospitalized due to acute medical illness have an increased risk for thrombosis and are therefore routinely given short duration VTE prophylaxis. Currently in the EU there is no approved or guideline-recommended anticoagulant indicated for extended VTE prophylaxis beyond the 10 ± 4 days of standard therapy.

Three prior studies in extended thromboprophylaxis in hospitalized AIM patients, EXCLAIM, ADOPT, and MAGELLAN, did not succeed in demonstrating a positive benefit: risk ratio or a reduction in clinically important symptomatic events with enoxaparin, apixaban, and rivaroxaban, respectively. Furthermore, in the American College of Chest Physician's recommendation it is stated that "in the acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis, we suggest against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay" (Chest Journal 2012).

3.1.1. Disease or condition

3.1.2. Available therapies and unmet medical need

The interest in the proposed indication derives from previous randomized trials and observational studies that have shown that the risk of VTE, including VTE related death following hospitalization continues in high risk AIM patients after discontinuation of short duration (10 ± 4 days) VTE prophylaxis with parenteral anticoagulants such as enoxaparin.

3.1.3. Main clinical studies

The development programme for betrixaban includes three phase II studies pertaining to indications that are approved for the other, already authorized, oral direct factor X inhibitors. Study PN006 included subjects with Atrial Fibrillation/Atrial Flutter, study 05-003 (EXPERT) included Total Knee Replacement patients and study 08-015 (EXPLORE) included subjects with documented non-valvular AF with an indication for anticoagulation with a vitamin K antagonist. Pharmacologic and safety data can be extracted from these studies but very limited conclusions regarding the efficacy of betrixaban for the currently proposed indication.

The main study in support of this application was the APEX study. This was a large phase III study, randomized, double-blind, parallel group, multicentre and active controlled superiority study for the prevention of VTE in patients who are at risk due to acute medical illness.

Betrixaban was administered over an extended duration (35 to 42 days) and the active control was 10 ± 4 days of parenteral enoxaparin, the standard of care. Patients that had GFR<30 as well as patients on P-gp inhibitors received 40 mg betrixaban daily (after a 80 mg loading dose) while the rest of the patients received 80 mg (after a 160 mg loading dose).

Patients were eligible for the APEX study if they were hospitalized for specified acute medical illness; acutely decompensated heart failure, acute respiratory failure in patients with chronic symptomatic lung disease, acute infection without septic shock, acute rheumatic disorders (including acute lumbar pain, sciatica, vertebral compression, rheumatoid arthritis, systemic lupus erythematosus) or acute ischemic stroke, had reduced mobility. In addition, according to the finally adopted criteria, the patients should have any one of the following risk factors for VTE: a. ≥ 75 years of age, or b. 60 through 74 years of age with D-dimer ≥ 2 x ULN, or c. 40 through 59 years of age with D-dimer ≥ 2 x ULN and a history of either VTE or cancer.

Betrixaban was compared to enoxaparin through a closed testing, gate-keeping procedure that sequentially, in a hierarchal order, tested the primary and secondary efficacy composite outcome hypothesis in each of the three defined Cohorts in seven steps to ensure control of the study-wise Type I error. Cohort 1 included patients who have D-dimer≥2 x ULN at baseline and Cohort 2 included patients who have D-dimer≥2 x ULN and/or age≥75 years. The last cohort of patients was the Primary Efficacy Outcome Population (PEOP) which included all patients in the mITT population with available assessment of all components of the primary efficacy outcome endpoint. The mITT population consisted of all patients who had taken at least one dose of study drug and who had follow-up assessment data on one or more primary or secondary efficacy components.

3.2. Favourable effects

The primary outcome was a composite endpoint and constituted of the occurrence of any of the following events through Visit 3 (i.e. up to Day 47): Asymptomatic proximal DVT (as detected by ultrasound), Symptomatic DVT (proximal or distal), Non-fatal PE, or VTE-related death. The event rates (95% CI) % for step 1 in the primary analysis in Cohort 1 was 8.5 (7.3-9.7) % in the enoxaparin arm and 6.9 (5.8-8.0) % in the betrixaban arm (p=0.054). Thus, superiority vs standard of care with Enoxaparin was not formally demonstrated for Betrixaban. Using the point estimates for the event rates in the two groups, the absolute risk reduction is by the assessor calculated to be 1.6%, yielding a NNT of 63.

The applicant conducted an alternative analysis of the primary efficacy endpoint based on the post-hoc PEOP including one additional patient (patient X) in the enoxaparin arm who had an event whereby the

p-value in the analysis of Cohort 1 changed from 0.054 to 0.048. The applicant considered that inclusion of this event and which was based on clinical evaluation in accordance with the intent of the SAP yields a p-value supporting formal evaluation of Cohort 1 and the entire study population.

In Cohort 2 and the overall population the nominal p-values for the comparison between betrixaban and the comparator are lower than in Cohort 1 (and below 0.05).The event rate (95% CI) % for the primary efficacy analysis in the overall primary efficacy population was 5.3 (4.5-6.1) % for Betrixaban and 7.0 (6.1-7.9) % for the comparator (nominal p-value=0.006). However it was noted that the ARR using the point estimate are similar in Cohort 1, Cohort 2 and the overall population.

The primary efficacy outcome in Cohort 1 was also analysed in pre-specified subgroups. In the analysis by dosing criteria, patients with neither severe renal insufficiency nor need for a strong P-gp inhibitor randomized to 80 mg betrixaban had an event rate of 6.3% vs. 8.4% in patients receiving enoxaparin (nominal p = 0.026).

For patients with severe renal insufficiency, the event rate was 10.2% in the betrixaban group (11/108) vs 12.7% in the enoxaparin group (10/79) (nominal p=0.598). For patients on strong P-gp inhibitors, the event rate was 8.5% (29/342) in the betrixaban group vs 7.9% (28/356) in the enoxaparin group (nominal p=0.767).

The first secondary efficacy analysis included only symptomatic events. The event rates (95% CI) % for Cohort 1 in the analysis of the first secondary efficacy endpoint was 1.3 (0.8-1.8) % for betrixaban and 1.9 (1.4-2.5) % for the comparator (nominal p-value 0.092). The event rates (95% CI) % were 0.9 (0.6-1.3) % for betrixaban and 1.5 (1.1-1.8) % for the comparator in the overall population (nominal p-value= 0.039)

The second secondary endpoint was coherent with the composite primary efficacy endpoint except that VTE-related death was exchanged for all-cause mortality. The event rate (95% CI) % for the second secondary efficacy outcome in Cohort 1 was 11.5 (10.1-12.9) % for betrixaban and 12.9 (11.4-14.3) % for the comparator (nominal p-value=0.164).The event rate (95% CI) % in the overall population was 9.2 (8.2-10.2) % for betrixaban and 10.9 (9.8-11.9) % for the comparator (nominal p-value=0.024).

3.3. Uncertainties and limitations about favourable effects

Several aspects of the design of the APEX study make it difficult to define the target population that would benefit from prolonged treatment with betrixaban with sufficient certainty: the critical place of D-dimer testing in the assessment of whether patients were eligible to the study, the many amendments of the inclusion and exclusion criteria that were implemented during the course of the study, questions pertaining to the immobilization status and severity of the acute medical illness of the included subjects. Moreover, the absence of patients with active cancer constitutes a lack of data in a population at high risk of both VTE and bleeding.

Betrixaban was not shown to be superior to enoxaparin, according to the pre-specified closed testing, gate-keeping procedure in Cohort 1. Even accepting the alternative analysis including patient X which showed a borderline statistical significance, it raises significant concerns over the robustness of the reported results. The APEX study was a large study including thousands of patients statistical significance should not be affected by the inclusion or exclusion of one patient in the analysis. This is even more important in the context of a new treatment with no established evidence in any indication and which is trying to establish a new treatment paradigm with the applied indication.

There is further uncertainty due to the fact that a rather large fraction of the randomised patients in both treatment groups of the APEX study were not included in the primary efficacy population as they did not have an evaluable ultrasound result between Day 32 and Day 47 (and no symptomatic event). This number was higher in the betrixaban group than in the comparator group. The overall high rate of ultrasound drop-outs and the difference in ultrasound drop-out rates between the groups could influence the outcome of the primary endpoint.

The applicant explored the issue of missing data by providing sensitivity analyses using multiple imputation to handle those with missing assessments under two different underlying assumptions about the missing data. In the Missing At Random analysis (excluding patient X) the results for the primary endpoint were; for Cohort 1: ARR = 1.6% and p = 0.11 and in the overall population: ARR = 1.7% and p = 0.008, and thus quite similar to the outcome in the primary analysis of the primary endpoint. In the Jump To Reference analysis (excluding patient X) the results were for Cohort 1: ARR= 1.31 and p-value=0.219 and for the overall population: AR= 1.46 and p-value=0.027, i.e. smaller compared to the outcome in the primary analysis of the primary endpoint. From these analyses; it is evident that the findings in Cohort 1 are not robust.

3.4. Unfavourable effects

Major bleeding occurred with similar frequencies in the two treatment groups, (0.67% vs. 0.57% in the betrixaban and enoxaparin arms, respectively), but CRNM [clinically relevant non major] bleedings were more frequent in the betrixaban group (2.45% [95% CI 1.95; 2.95] vs. 1.02% [0.70; 1.35]). CRNM bleedings included haematuria, epistaxis, rectal and upper GI bleedings. Therefore, in the composite of Major or CRNM bleedings, there was a clear difference in the incidence of these events in favour of enoxaparin (3.12 vs 1.59%, nominal p-value <0.001).

Approximately 50% of the CRNM bleedings in both groups were classified as severe adverse events (n=46 vs. 18 in the betrixaban and enoxaparin groups, respectively).

Head to head comparison of betrixaban vs standard of care showed an increased risk of major or CRNM bleeding with betrixaban in the first 14 days of the APEX study, i.e. during the period when all patients where on anti-coagulant treatment.

The incidences of Major and CRNM bleedings requiring hospitalization were slightly higher in the betrixaban group than in the enoxaparin group, 0.97 vs. 0.78%, respectively. According to the follow-up information in the overall safety population the numbers of Major or CRNM bleeds that required medical/surgical consultation were 94 vs. 50 in the betrixaban and enoxaparin groups, respectively, medical/surgical intervention 41 vs. 22, hospitalization 23 vs. 14, study drug interruption 18 vs. 4 and study drug discontinuation 68 vs. 38, respectively.

In the 80 mg dose group the ARR of Major and CRNM bleedings for enoxaparin compared to betrixaban is less (-1.07%), compared to the whole trial population (-1.53 %). The mortality rates were similar in the two treatment groups (6 %) and with similar distributions of adjudicated causes of death.

Differences between the two treatment groups of other adverse events were generally small and similar in the overall study population and in Cohorts 1 and 2.

3.5. Uncertainties and limitations about unfavourable effects

The higher incidence of clinically relevant bleedings among the betrixaban treated patients is of particular concern, especially due to the pharmacokinetic properties of betrixaban. Its longer half-life

compared to other oral anti-coagulants and the pronounced food effect might render the management of such events more problematic in this fragile and elderly target population.

In the 40 mg dose group the incidences of major or CRNM bleedings were 4.79 vs 1.38% in the betrixaban and enoxaparin groups, respectively (ARR -3.42, 95% CI -5.18, -1.65). It was agreed with the Applicant that the 40 mg dose group probably represents a more vulnerable subgroup of patients. However it is of some concern that despite the relatively higher incidence of thrombotic events in this lower dose group, to some extent probably due to a generally lower exposure of betrixaban than in the overall study population, the difference in bleeding rates vs. enoxaparin seems to increase. It is therefore difficult to draw any conclusions regarding a correlation between betrixaban plasma levels and the risk of bleeding.

As only one dose level was studied in APEX, information is lacking regarding the therapeutic window (exposure response on hard endpoints) of betrixaban. Without such information, any changes in plasma concentrations are hard to evaluate.

The relative increase in clinically relevant bleedings is approximately similar to the increases seen in the Adopt and Magellan studies of other Xa inhibitors (approximately doubled) where the B/R balance was considered negative. There are however remaining uncertainties on the relative antihaemostatic potency of betrixaban as compared to other Xa inhibitors. This is partly due to the limited clinical experience from betrixaban in other populations than the one now aimed for. There is however no reason to expect that the distribution of bleedings of different severity would be different for betrixaban than for other Xa inhibitors. Thus, in the large target population proposed by the applicant all kind of bleedings typically associated with Xa inhibition (including ISTH major bleedings) would be expected to increase to a similar extent in relative terms.

3.5.1. Effects Table

Table 46. Effects Table for betrixaban in the prophylaxis of venous thromboembolism (VTE) in adults hospitalised for an acute medical illness (data cut-off:15 January 2016)

Effect	Short Description	Unit	Betrixaban	Enoxaparin	Uncertainties/ Strength of evidence	References
Favourable Effects						
Composite endpoint: 1) Asymptomatic proximal DVT 2)Symptomatic DVT 3) Non-fatal PE, or 4) VTE-related death	Occurrence of any of the events through Visit 3 (=35 days ± 7 days)	% (95 % CI)	6.90 (5.8-8.0)	8.49 (7.3-9.7)	p=0.054. Statistical significance achieved in an alternative analysis including an additional patient in the control arm, p=0.048. Superiority of betrixaban not demonstrated	APEX, Cohort 1 of the PEOP
Unfavourable Effects						

Effect	Short Description	Unit	Betrixaban	Enoxaparin	Uncertainties/ Strength of evidence	References
Major or CRNM bleedings	Events occurring through 7 days after treatment discontinuation	%	3.12	1.59	Nominal p-value <0.001	APEX

Abbreviations: CRNM: Clinically Relevant Non-Major bleedings, DVT: Deep Vein Thrombosis, PE: Pulmonary Embolism, PEOP: Primary Efficacy Outcome Population

Notes: Betrixaban was compared to enoxaparin through a closed testing, gate-keeping procedure that sequentially tested the primary and secondary efficacy composite outcome hypothesis in each of the 3 Cohorts in seven steps. Cohort 1 included patients who have D-dimer ≥2 x ULN at baseline and Cohort 2 included patients who have D-dimer ≥ 2 x ULN and/or age ≥75 years. As superiority not demonstrated in Cohort 1, subsequent analyses were considered exploratory.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The pivotal APEX study was designed to show superiority of Betrixaban, administered over an extended duration (35 to 42 days) compared to short duration standard of care prophylaxis with Enoxaparin (10 ± 4 days) in patients that had been hospitalized for acute medical illness, in thrombosis prevention. The statistical test strategy set out by the applicant formally failed in showing superiority of Betrixaban over standard of care with Enoxaparin in the first Cohort tested (patients who have D-dimer ≥ 2 x ULN at baseline). Superiority appeared to be shown in the overall primary efficacy population, but the relevance of this analysis can be questioned considering that, when using the test procedure put forth by the Applicant, this analysis should be regarded as exploratory.

Using the point estimates for the event rates in the two groups for the primary efficacy analysis, the absolute risk reduction is calculated to as 1.6%, yielding a Number Need to Treat of 63.

It should be emphasised that only one pivotal study was conducted, which impacts on the level of certainty in the results required before these can be considered compelling both in terms of the degree of statistical significance and its clinical relevance. These requirements have not been satisfied by the results from the APEX study.

The applicant provided a number of possible explanations for the failure of the study. These explanations include inadequate dosing, especially of individuals with renal insufficiency and the use of suboptimal D-dimer testing for classifying study subjects. Whilst some of these explanations appear reasonable, this does not change the fact that the study did not formally meet its predefined primary endpoint and that efficacy superiority vs established standard of care has thus not been established and neither has superiority vs placebo. The data available seem to indicate a positive trend, but a trend that should preferably be confirmed in a second trial (in which the experience and acquired knowledge, for example on correct dosing for patients with renal failure could be of use for the planning and design of the study).

In addition to this, there are a number of other uncertainties and limitations of the data which affect the importance of the favourable effects observed. These pertain to the difficulties to define the intended target population as justified by available data, the potential impact that the many protocol amendments may have on the overall findings of the study, the interpretation/estimation of the primary efficacy outcome in light of the substantial amount of missing data on the primary efficacy endpoint and which are unevenly distributed among the treatment groups. The issue of missing data was explored through sensitivity analysis using different statistical approaches; the outcome however of these analyses confirmed the CHMP's view that the results, especially in Cohort 1 (which was the population in which the primary endpoint was to be tested according to the predefined statistical testing procedure), were not robust.

Regarding unfavourable effects, the most important risk in association with betrixaban use is the risk of bleeding. Major bleeding occurred similarly in both groups, but CRNM [clinically relevant non major] bleeding was more frequent in the Betrixaban group. The incidence of major bleedings is rather insensitive to differences in bleeding tendencies due to the rather conservative ISTH criteria applied. Thus, the overall bleeding pattern should be carefully considered.

CRNM bleedings included haematuria, epistaxis, rectal and upper GI bleedings. Approximately 50% of them were classified as SAE. The observed increased incidence of CRNM bleedings is of concern in the fragile, and often elderly, patients that can be expected to continue treatment for several weeks after discharge from hospital. Moreover, the comparatively slow elimination rate of betrixaban as well as the markedly increased exposure in fasting state may also have implications in minimising and managing the consequences of these events in clinical practice.

3.6.2. Balance of benefits and risks

From the data presented by the applicant, it is concluded, that the favourable effects of betrixaban in terms of VTE prophylaxis for the proposed indication and posology, do not outweigh the risks associated with this treatment i.e. the risk of bleedings. There is no strong evidence of a superior effect compared to enoxaparin and the increased risk of clinically relevant bleedings may translate into serious complications in the proposed target population which most likely will have both comorbidities and co medications. In addition, some of these patients could have a poor food intake which would potentially increase their risk of bleedings since taking betrixaban under fasting conditions is expected to increase exposure of the drug.

3.7. Conclusions

The overall Benefit/Risk of Dexxience is negative.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Dexxience in the prophylaxis of venous thromboembolism (VTE) in adults hospitalised for an acute medical illness who are at risk for thromboembolic complications due to restricted mobility and other risk factors for VTE, the CHMP considers by consensus that the safety and efficacy of the above mentioned medicinal product are not sufficiently demonstrated.

The CHMP considers that:

- The efficacy of Dexxience in the proposed indication has not been robustly demonstrated. Evidence presented was based on a single pivotal study in which the first step of the statistical testing (according to the pre-specified closed testing gate keeping procedure) of the primary endpoint did not yield a reliable result of compelling evidence of a true difference between the treatment groups. There is further uncertainty around the reliability of the results due to missing data.
- Treatment with Dexxience was associated with an increased risk of bleeding events (major or clinically relevant non major bleedings) compared to the comparator in the trial (both at 14 days in comparison to enoxaparin and at the end of the trial). This is a serious concern considering that the target population comprises patients with comorbidities for which potential bleedings may have serious consequences. This is further compounded by the pharmacokinetic properties of Dexxience, which could have significant implications for the occurrence and management of such events in clinical practice.

Due to the aforementioned concerns, a satisfactory summary of product characteristics, labelling, package leaflet, and risk management plan cannot be agreed at this stage.

5. Re-examination of the CHMP opinion of 22 March 2018

Following the CHMP conclusion that Dexxience was not approvable as its efficacy had not been robustly demonstrated and its use was associated with an increased risk of bleeding events which are of particular concern in the intended target population for this product, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Following a request from the applicant at the time of the re-examination, the CHMP convened a Scientific Advisory Group (SAG) inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the applicant's response.

Detailed grounds for re-examination submitted by the applicant

The applicant presented in their submission the following grounds for re-examination:

Ground #1: Clinical burden

- There is an urgent unmet medical need for a new anticoagulant which would be administered to acutely ill medical patients during their entire hospitalisation and extending beyond hospital discharge for 35-42 days. In the EU annually an estimated 275,000 non-fatal VTE events and 90,000 VTE-related deaths occur in acutely ill medical patients because the efficacy and safety of standard injectable agents is limited to a short duration and is based on studies in moderate risk patients. Most of the VTEs and VTE-related deaths occur after a short duration of therapy or following hospital discharge in high risk patients and there are no anticoagulants approved for VTE prophylaxis beyond 6 to 14 days. Over the past 2 decades efforts to address this unmet need have demonstrated some efficacy but this has come at the cost of excess major bleeding. Betrixaban is administered for 35 to 42 days, covering the time of high risk for these patients.

Summary of the Applicant`s position:

In prior feedback, the CHMP acknowledged an unmet need for the proposed indication. Quoting from the SAG meeting 18th December 2017 minutes:

"*There was general agreement that there is unmet medical need for prolonged thromboprophylaxis in acutely ill medical patients. It was acknowledged that the risk of thrombotic events for patients requiring anticoagulation extends beyond 10-14 days. Importantly the Group noted that this risk could be particularly relevant for patients who are discharged early, i.e. after 4-5 days, and who as a result may discontinue their anticoagulant prophylaxis on discharge. The concept to extend the thromboprophylactic treatment beyond 14 days is attractive in principal but risks must be carefully considered."*

Despite standard-of-care agents available, more than 275,000 VTE events, including an estimated 90,000 VTE-related deaths, occur in this population annually in the EU. Approximately half of the VTE events occurs after hospital discharge and hence after standard in-hospital thromboprophylaxis. Although betrixaban is approved in the USA, no therapeutic agent is currently approved in the EU or recommended in guidelines for the high risk period of 42 days following hospital admission.

According to the applicant's estimate there are 4.7 million medical patients hospitalised annually in the EU who are similar in their risk profile to the patients in APEX who were randomized to 80 mg betrixaban.

Extrapolation of the efficacy and safety results in APEX to this EU population, and assuming use of 35 to 42 days of betrixaban rather than 6 to 14 days of enoxaparin, would yield the following projected annual effects in the EU:

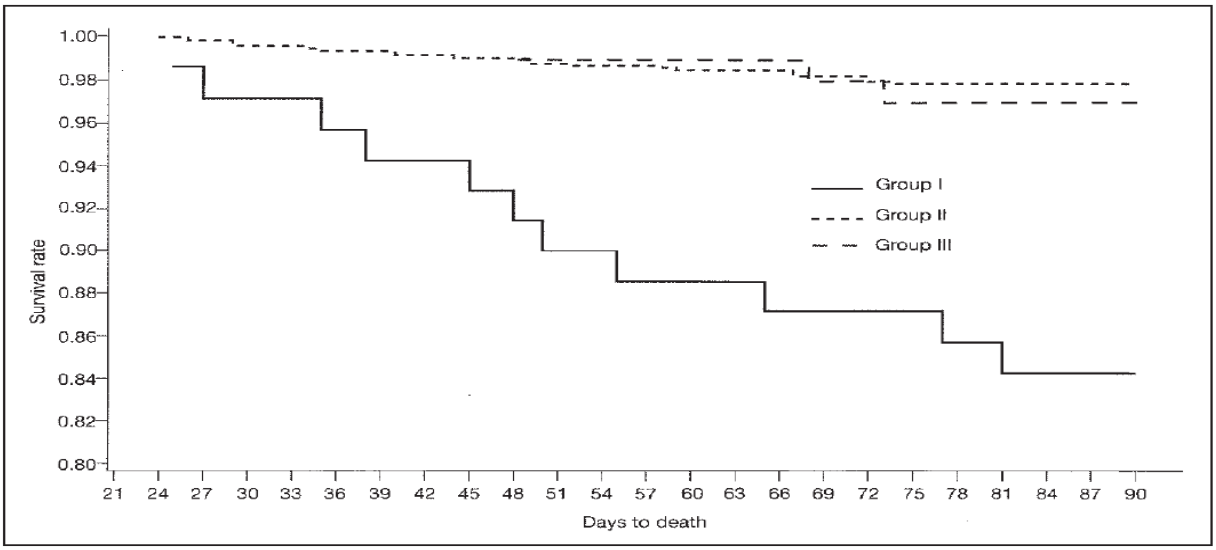
- 79,900 fewer asymptomatic VTE events
- 42,770 fewer symptomatic VTE events
- 12,690 fewer VTE-related deaths
- 37,130 fewer VTE-related hospitalisations
- 52,170 additional CRNM bleeding events of which only 1,410 will require hospitalisation
- No increase in major bleeding events
- Numerically fewer fatal or intracranial bleeding events

The majority of primary efficacy events in APEX were asymptomatic proximal DVTs detected by ultrasonography. While some people dismiss the importance of these events because they are not associated with acute symptoms, their longer term impact is clinically meaningful. In both PREVENT (dalteparin vs placebo for VTE prophylaxis in medical patients; **Figure 14**) and APEX (**Figure 15**), these asymptomatic events were associated with a ~5-fold increase in mortality after hospital discharge compared to patients without a DVT.

Figure 12. Kaplan-Meier Survival Curves from Day 21 to Day 90 in PREVENT Trial

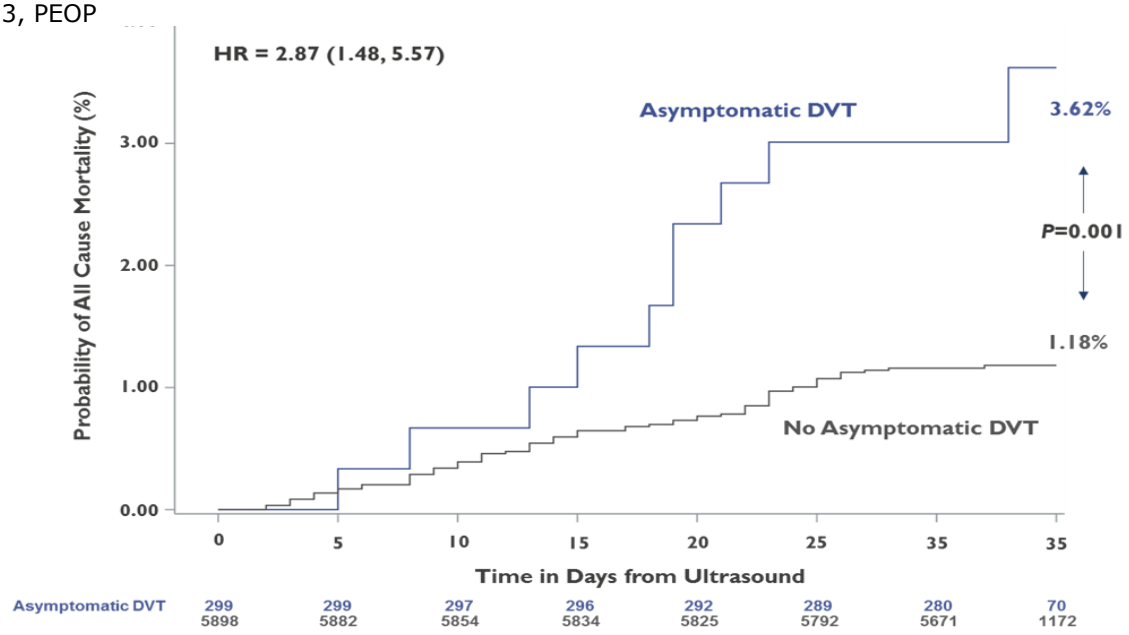
Analysis of 1,738 Acute Medical Patients in the PREVENT Study with No Symptomatic Event at Day 21

- 90 Day Mortality – 13.75% with Asymptomatic Proximal DVT (Group 1)
- 3.39% with Asymptomatic Distal DVT (Group II)
- 1.92% without DVT (Group III)



Source: Vaitkus, et al: Clinical relevance of asymptomatic DVT. Thromb Haemost 2005;93:76-9. [4]

Figure 13. Time to All-Cause Mortality After Ultrasound in Patients Without a Symptomatic VTE at Visit 3, PEOP



Therefore, asymptomatic proximal DVT are a clinically important outcome; these patients had measurable clot in proximal lower extremity veins at the end of the treatment period with the potential for these clots to enlarge and/or embolise, or both.

When detected incidentally most physicians treat these clots in the same manner as they treat symptomatic DVT. The effect of treatment of these asymptomatic VTE is clearly seen in the Kaplan-Meier curves with a diminution in symptomatic VTE event rates following the diagnostic ultrasound scans.

The net benefit from extended prophylaxis is both substantial and underappreciated largely because of the absence of an approved therapy for these patients despite almost 2 decades of effort to address this unmet need. Betrixaban has the potential to deliver significant reductions in patient morbidity and mortality and an associated reduction in medical resources and costs to manage these patients in the EU. A 35 to 45% relative reduction would lead to an estimated 10% absolute reduction in the burden of VTE.

Ground #2: Overall Efficacy of Betrixaban in APEX

- Outcomes in the overall APEX population are the best estimate of the efficacy, safety and net benefit of betrixaban and constitute an appropriate formal analysis (and not an exploratory analysis) to assess efficacy because the APEX trial met its primary endpoint in the D-dimer subpopulation (Cohort 1). The CRO and ARO analyses datasets were developed separately and simultaneously prior to database lock. The CRO dataset was compiled in error and ARO dataset was compiled correctly and we've corrected the CRO mistake published in the initial NEJM in the AHJ publication.

  The APEX primary endpoint findings in both the PEOP and mITT populations were statistically significant in the overall population ($p = 0.005$ and $p = 0.003$, respectively). The totality and consistency of APEX study results are strongly supportive of betrixaban approval. Betrixaban administered for 35 to 42 days compared to standard of care with enoxaparin administered for 6 to 14 days demonstrated statistically significant reductions in: (a) total VTE including VTE-related death; (b) symptomatic VTE including VTE-related death; (c) VTE-related re-hospitalisation; and (d) ischemic stroke. These clinically meaningful and statistically significant reductions in efficacy outcomes that occurred on betrixaban were achieved without an increase in major bleeding (in contrast to prior studies) and with fewer intracranial haemorrhages. To the sponsor and academic leadership of APEX, the favourable benefit-risk profile of betrixaban is unequivocal.

Summary of the Applicant's position:

The applicant noted the continued concern from CHMP on the statistical outcome in Cohort 1 of the APEX trial and provided a letter from the APEX Executive Committee (EC) in which according to their interpretation of the SAP, Patient X (See also Section 2.5.2 of this report) should have been counted as having a primary endpoint event.

Relevant sections of the Statistical Analysis Plan in Determining Whether Patient X Should Count as an Event

Study Endpoints

Symptomatic events for the primary analysis must occur on or before Day 42 or the day of Visit 3, if Visit 3 occurs before Day 42. Such events must meet both criteria for patients who have a Visit 3: on or before Day 42, and on or before the day of Visit 3. Supportive analyses may use different Day ranges.

An asymptomatic event detected the same Day as onset of a symptomatic DVT, or within two days after onset of a symptomatic DVT, will not be considered a separate event. It will be concluded that

the two events detected the same physical issue, and is likely to happen because the CUS that is used to confirm diagnosis of a symptomatic DVT might also be sent to the ultrasound central lab for adjudication. If an asymptomatic event is detected on the same Day as, or within two days after, onset of a symptomatic DVT, only the symptomatic DVT will be included in analyses as an event.

Primary Efficacy Outcome

The primary (composite) outcome is the occurrence of any of the following events through Visit 3: Asymptomatic proximal DVT (as detected by ultrasound), symptomatic DVT (proximal or distal), non-fatal PE, or VTE-related death.

All events are as adjudicated by the CEC except asymptomatic proximal DVT (as detected by ultrasound) which will be determined by the ultrasound core laboratory. For the primary efficacy analysis: Compression ultrasound (CUS) results will be used if the ultrasound shows an asymptomatic event and it occurred any time after randomization and on or before Day 47.

- CUS results will be used if the ultrasound showed no event and it occurred during the window from Day 32 to 47.
- Symptomatic events will be used if the onset is on or before Day 42 or the date of Visit 3, if Visit 3 occurred before Day 42.

The windows for analysis of CUS were widened from the windows requested in the protocol. A patient with an asymptomatic event at any time Day 1 to 47 is at increased risk of a thrombotic event and thus such will count as events. A patient with CUS that shows no asymptomatic DVT on Days 32 to 34 or 43 to 47 is likely to have had the same result, had the CUS been obtained in the window requested in the protocol. Additionally, in Amendment 3, it was noted that a patient could have the CUS performed as late as Day 47 because the CUS was often to be scheduled at a different physical location than other Visit 3 activities. Sensitivity analyses described later in this document will use other Day range windows for the CUS component of the primary efficacy endpoint to confirm the robustness of primary analysis.

Patient X

Patient X had a protocol mandated Visit 3 on Day 35 at which time the subject reported no symptoms. A protocol mandated ultrasound was then performed on Day 38 in the evening. This ultrasound was positively adjudicated by a central core laboratory as showing thrombosis. This ultrasound preceded the reporting of a symptomatic VTE event later that Day. This event was adjudicated as a VTE event by the independent CEC at DCRI. The patient had a repeat ultrasound on Day 40, and the military time of this ultrasound is not known. This second ultrasound was positively adjudicated by the central core laboratory as showing thrombosis.

Members of the EC were provided with the language from the statistical analysis plan and the patient narrative and were asked to review the documents independently.

The first line of the SAP states the following: Symptomatic events for the primary analysis must occur on or before Day 42 or the day of Visit 3, if Visit 3 occurs before Day 42. All members interpreted the first line of the SAP as indicating that a symptomatic event occurring on Day 38 would meet these criteria. The first line of the SAP does not explicitly exclude an event occurring between Visit 3 and Dav 42.

Even if the first sentence of the SAP were alternatively interpreted that a symptomatic event between Visit 3 and Day 42 would not count as a primary endpoint, all members of the EC indicated that at

least the first ultrasound would count towards the primary endpoint. In this scenario, no symptomatic event would have been deemed to have occurred on Day 38. From a Boolean logic or coding perspective, since no symptomatic event occurred, there was therefore no symptomatic event that would invalidate the inclusion of a positive ultrasound on the same day of or 2 days after the symptomatic event. The ultrasounds would therefore count toward the primary endpoint.

While no members of the EC drafted the language in the SAP, all members felt that the author would not intend to draft an SAP in such a way that it would be interpreted in such way that a patient who had 3 positively adjudicated events before Day 42 would not count as an event. In the assessment of multiple events or recurrent events (an exploratory endpoint), language pertaining to the exclusion of an ultrasound event due to the fact that it was neither temporally nor anatomically independent of a symptomatic clinical venous thrombotic event occurring in the same limb is relevant. It could be argued, however, that a positive ultrasound and a pulmonary embolism constitute separate events: the ultrasound constituting the detection of the initial nidus of the thrombosis, and the pulmonary embolism constituting a distinct episode of embolism from this initial nidus of thrombus. This is similar to heart failure with left ventricular thrombus or left atrial appendage clot due to atrial fibrillation and embolic stroke counting as 2 separate events. Despite the potential relevance or a positive ultrasound in a scenario or multiple events, the simultaneous occurrence or 2 events, a positive ultrasound and a symptomatic event has no relevance in determining if a patient had a single primary endpoint event. If any event of the components of the primary endpoint occurs, that event should be counted.

The EC had not reviewed the emails from DCRI to Portola prior to the conference call. It is important to note that the EC independently offered a similar interpretation as DCRI, albeit after database lock. Importantly, the PERFUSE study group offered a similar interpretation as DCRI, prior to database lock and unblinding. It should be noted that it was the decision of the sponsor to accept the interpretation of PPD and not the independent academic research organizations. The EC has prepared this memo to the file as all members feel that the data adds importantly to the totality of evidence.

The applicant also provided a letter from three statisticians which state that the predefined hierarchy in testing is considered an unusual feature. "For APEX, as for any trial, we start from three key premises: 1) analysis by intention-to-treat should be the main focus of the primary endpoint; 2) the totality of evidence in all randomized patients provides the most reliable approach to drawing conclusions from the trial; and 3) the analysis should include all primary endpoint events known to have occurred at the time of database lock … We find it unusual to test the all-randomized patients (Cohort 3) only after two subgroups show statistical significance." It was further stated that the treatment effect on a relative scale did not depend on the patient´s D-dimer level, interaction test p = 0.28 and p = 0.59 using local and central laboratory values, respectively. "Thus, the data show no evidence that D-dimer level (or indeed any other patient characteristic) is an effect modifier, and hence subgroup analyses lead to no change to the above conclusion regarding the totality of evidence." The statisticians state: "Thus, we feel the emphasis on Cohort 1 was misguided; had we been involved in the statistical planning for this trial we would have argued for having the test in Cohort 3 represent the primary assessment of efficacy." Further: "On this basis, the primary efficacy outcome in APEX occurred in 5.30% of betrixaban patients and 7.06% enoxaparin patients, for a relative risk reduction of 24.3% (95% CI 8.1-37.7%); p = 0.005. The estimated absolute risk reduction is 1.75% (95% CI 0.56-2.94%) and the number needed to treat is 57 (95% CI 34-179). Conventional interpretation of the totality of data for the primary endpoint would conclude that the data show strong evidence for the superiority of betrixaban over enoxaparin. Superiority was shown in the context of the trial hypothesis which tested a new drug and simultaneously a new strategy, that is betrixaban administered for 35 to 42 days compared to standard 6 to 14 days of enoxaparin."

Objectively, an ultrasound-detected proximal DVT occurred in a patient within the protocol-specified time window and therefore should be included in the PEOP analysis population and counted as a study outcome event. Adjudication of this event and its inclusion in the consequent academic centre analyses all happened prior to database lock and unblinding. To exclude this event from the previously reported analyses was a mistake which was corrected and published in the American Heart Journal. Including this event resulted in a p-value of 0.048 in Cohort 1, and thus enabled continued hierarchical testing in the pre-specified PEOP population (**Table 52**).

Table 47. Primary Efficacy Outcome (Asymptomatic DVT, Symptomatic DVT, Non-Fatal PE, VTE-Related Death) – PEOP, APEX Study

Betrixaban % (95% CI) [1]	Enoxaparin % (95% CI) [1]	Relative Risk Reduction[2] and 95% CI	p-Value [3]	ARR [4] (%) and 95% CI	NNT [5]
Primary Efficacy Outcome Population - Cohort 1					
6.90 (5.76, 8.03)	8.53 (7.30, 9.77)	0.198 (0.002, 0.356)	0.048	1.64 (-0.04, 3.32)	62
Primary Efficacy Outcome Population - Cohort 2					
5.63 (4.78, 6.48)	7.08 (6.15, 8.02)	0.204 (0.027, 0.348)	0.025	1.45 (0.19, 2.72)	69
Primary Efficacy Outcome Population					
5.30 (4.51, 6.09)	7.06 (6.16, 7.95)	0.243 (0.081, 0.377)	0.005	1.75 (0.56, 2.94)	57

Note: Cohort 1 includes patients with D-dimer ≥ 2 x ULN as determined by the local lab. Cohort 2 includes patients with D-dimer ≥ 2 x ULN as determined by the local lab and/or age ≥ 75 years.

1 Event rate is based on the total number of patients in the respective cohort and analysis population in each treatment group.

2 Relative risk reduction is calculated as 1 – Relative risk.

3 Mantel-Haenszel test stratified by the dosing criteria and entry criteria

4 Absolute Risk Reduction: event rate difference (enoxaparin - betrixaban).

5 Number needed to treat: 1/ARR

Similarly robust results in all 3 study cohorts are found in the mITT population (**Table 53**) and in Cohort 1 with the central D-dimer analyses (rather than the less reliable local D-dimer results; **Table 54**). In Cohort, 1, there is no significant interaction between treatment and D-dimer (whether local or central, p = 0.277 and p = 0.558, respectively, Breslow-day test for homogeneity) and as is the case in general for subgroup analyses, the overall evidence in the total study population provides the most robust finding for treatment efficacy. As noted in EMA/CHMP/539146/2013 Guidance on the investigation of subgroups in confirmatory clinical trials, 'A reassuring pattern of results is where all point estimates from subgroup analyses are rather similar to the overall effect with all confidence intervals overlapping with the confidence interval for the overall effect.'

Table 48. Analysis of Primary Efficacy Endpoint in mITT Population

Population	Betrixaban n/N (%)	Enoxaparin n/N (%)	RR (95% CI)	ARR (95% CI)	RRR (95% CI)	p-Value	NNT
mITT, 80/40 mg Combined							
Cohort 1	132/2,314 5.70 (4.76, 6.65)	166/2,313 7.2 (6.12, 8.23)	0.791 (0.634, 0.987)	1.47 (0.06, 2.89)	0.209 (0.013, 0.366)	0.038	68
Cohort 2	160/3,407 4.7 (3.99, 5.41)	204/3,391 6.02 (5.22, 6.82)	0.784 (0.641, 0.959)	1.32 (0.25, 2.39)	0.216 (0.041, 0.359)	0.018	76
Overall	165/3,721, 4.43 (3.77, 5.10)	223/3,720 5.99 (5.23, 6.76)	0.746 (0.613, 0.908)	1.56 (0.55, 2.57)	0.254 (0.092, 0.387)	0.003	65

Table 49. Analysis of Primary Efficacy Endpoint Using Central D-dimer in PEOP Population

Population	Betrixaban n/N (%)	Enoxaparin n/N (%)	RR (95% CI)	ARR (95% CI)	RRR (95% CI)	p-Value	NNT
PEOP, 80/40 mg Combined							
Cohort 1	18/1838 6.42 (5.30, 7.54)	166/1823 9.11 (7.79, 10.43)	0.701 (0.558, 0.879)	2.69 (0.95, 4.42)	0.299 (0.121, 0.442)	0.002	38
Cohort 2	154/2741 5.62 (4.76, 6.48)	199/2772 7.18 (6.22, 8.14)	0.749 (0.609, 0.921)	1.56 (0.27, 2.85)	0.251 (0.079, 0.391)	0.006	65
Overall	165/3112 5.30 (4.51, 6.09)	224/3175 7.06 (6.16, 7.95)	0.724 (0.593, 0.883)	1.75 (0.56, 2.94)	0.276 (0.117, 0.407)	0.001	57

The approval of betrixaban is supported by the ARO analysis, including a p-value of 0.048 in Cohort 1. The assessment of APEX should not hinge on the outcome in one patient or on the outcome in a subgroup (i.e., Cohort 1) in an unconventional gate-keeping sequence (i.e., starting with a subgroup rather than the overall population) but instead should rely on the totality of the data in the overall population. APEX was a high quality study addressing an important unmet need and when taken at face value in any conventional analysis is a clearly positive trial. In the overall PEOP population and in other analyses of the overall population we have highlighted, the p-value is < 0.01, a level of evidence that is generally regarded as strongly indicative of a genuine treatment difference.

Further support of the compelling efficacy for betrixaban is provided by statistically significant time-to event analyses summarized in the forest plot of hazard ratio and 95% CI (**Figure 16**), and presented individually as KM curves for symptomatic VTE including VTE-related death (**Figure 17**), VTE-related rehospitalisation (**Figure 18**), ischemic stroke (**Figure 19**), VTE related mortality (**Figure 20**), and for all fatal or irreversible events **Figure 20**), all of which are clinically important and have a substantial impact on public health.

Figure 14. Forest Plot for Time to Event Efficacy Outcomes, Combined 80/40 mg Doses (mITT)

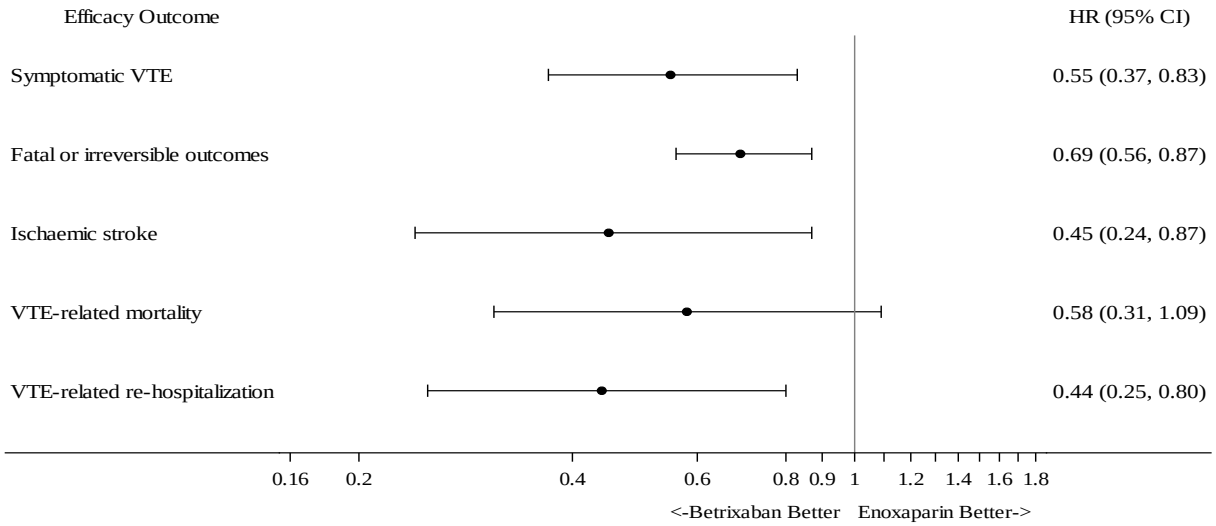


Figure 15: Time to Symptomatic VTE Event, Combined 80/40 mg Doses (mITT)

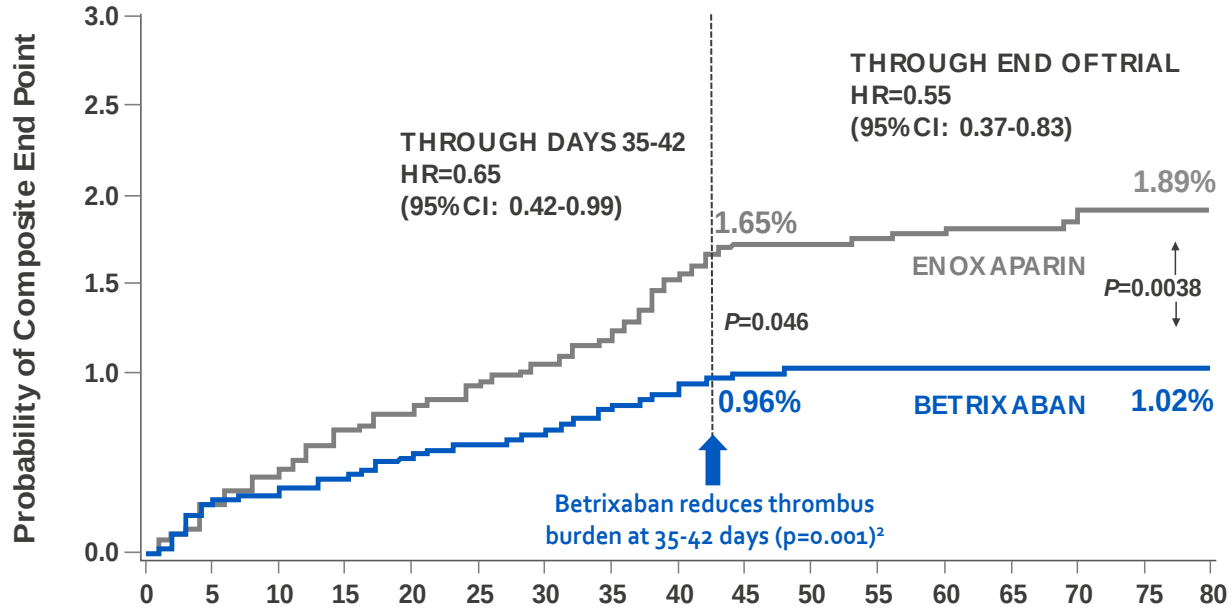
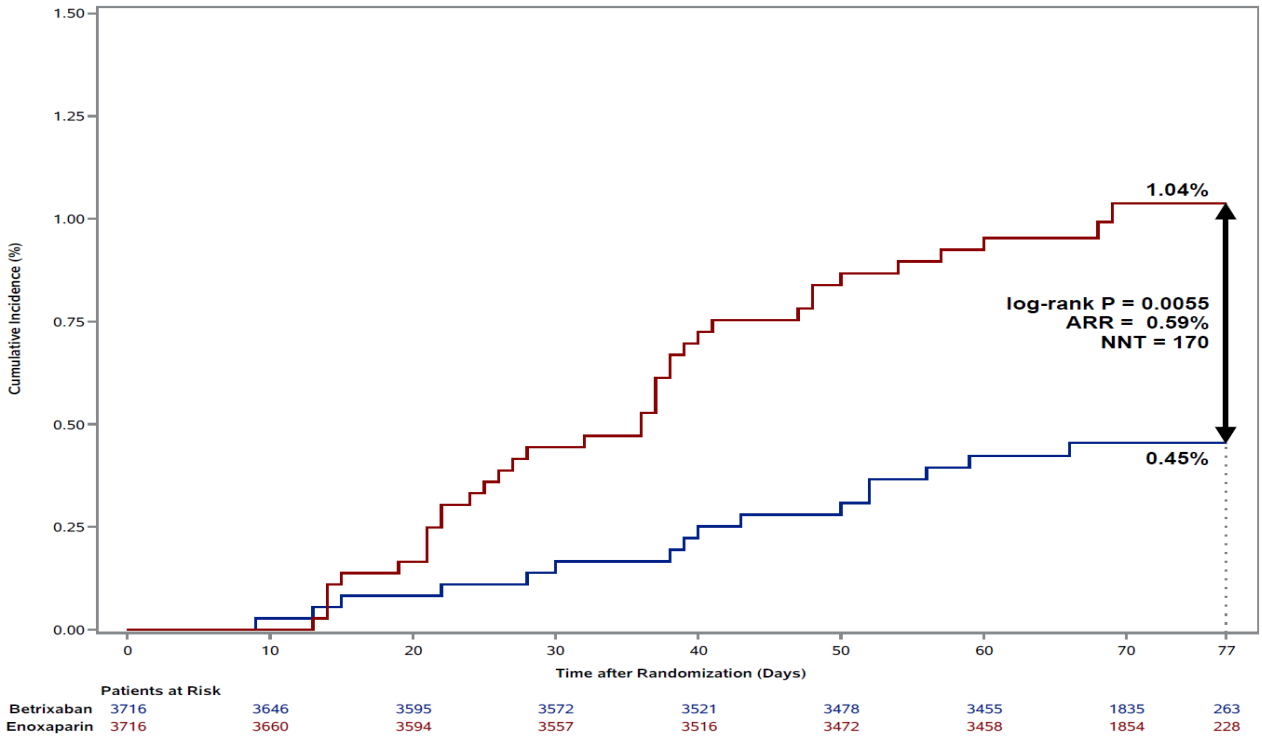
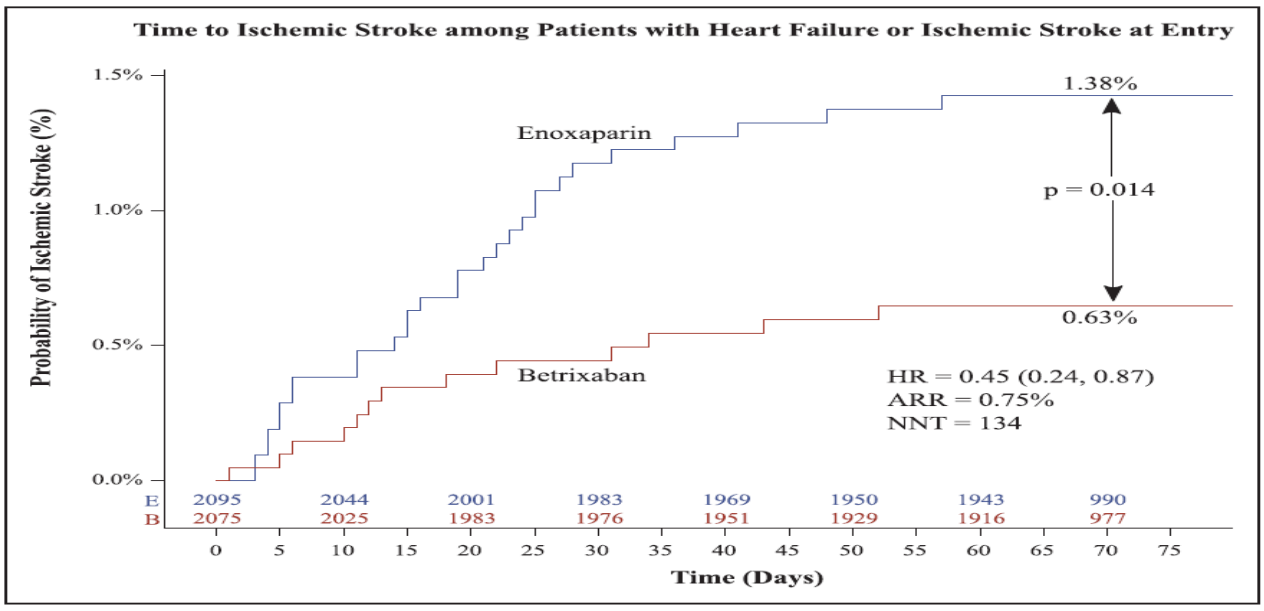


Figure 16. Time to VTE Related Re-hospitalization, Combined 80/40 mg Doses (mITT)



Source: Chi et al. *Circulation.* 2018; 137:91–94. [5]

Figure 17. Time to Ischemic Stroke in Patients with Ischemic Stroke or CHF as Index Event, Combined 80/40 mg Doses (mITT)



Source: Gibson CM et al. *Circulation*. 2017;135(7):648-655. [6]

Figure 18. Time to VTE Related Mortality, 80/40 mg Dose (mITT)

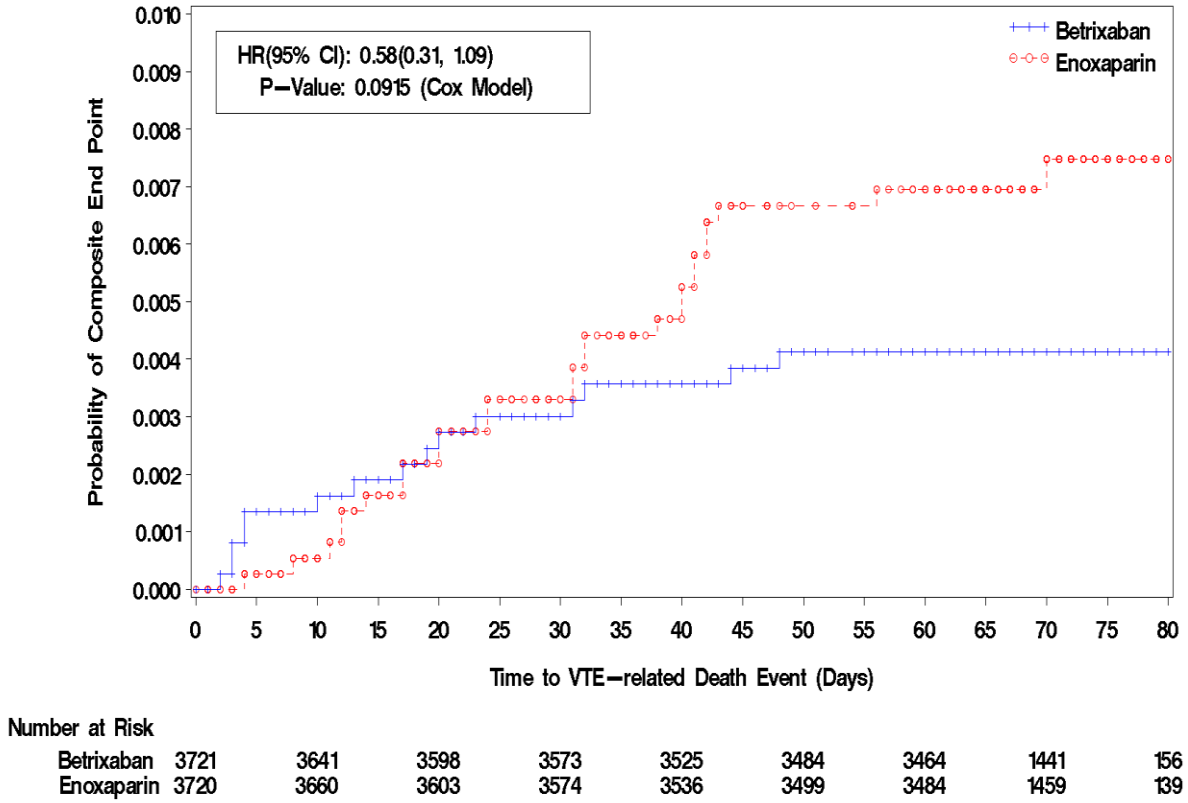
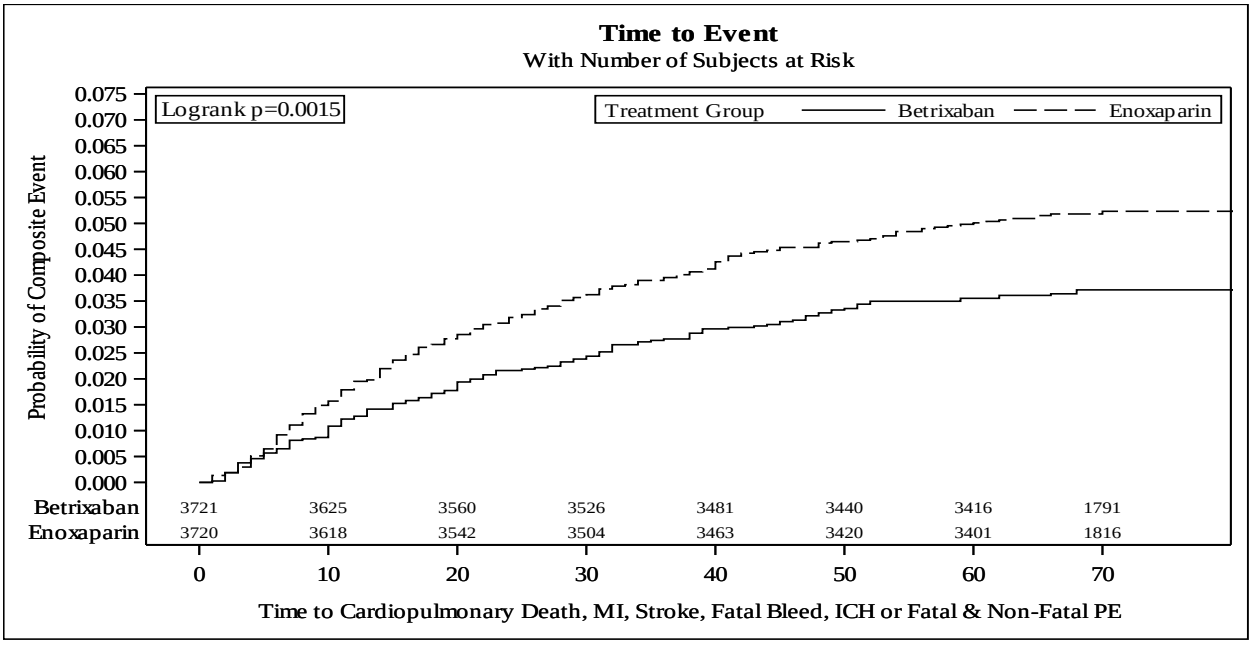


Figure 19. Time to Fatal and Irreversible Events, Combined 80/40 mg Doses (mITT)



The clinical utility of longer duration thromboprophylaxis as well as the unmet need uniquely addressed by betrixaban are visually apparent from each of the Kaplan-Meier plots in that the majority of events occurs well beyond the first 10 days of treatment (i.e., into the post-discharge period) and that most of the benefit conferred by betrixaban is beyond the first 10 days of treatment. The end-of-treatment

ultrasound examinations (Day 35-42) demonstrated that betrixaban substantially reduced the thrombus burden compared with enoxaparin (p = 0.012). The presence of thrombus at the time of the ultrasound increased the likelihood of subsequent mortality The totality of evidence from APEX offers strong support for the primary objective of the study which was to protect acutely ill medical patients during and beyond the hospitalisation period from venous thromboembolism.

Ground #3: Benefit-risk profile

- A favourable benefit-risk profile exists for betrixaban in the overall (80/40 mg) population. In APEX, patients were stratified at study entry based on clinical characteristics (presence or absence of severe renal insufficiency defined as CrCl < 30 mL/min, or concomitant use of strong P-gp inhibitors). A population in which to further assess the positive benefit risk is the stratum (80 mg) excluding patients with severe renal impairment or those taking strong P-gp inhibitors. The efficacy results for the 80 mg stratum were statistically significant in Cohort 1 and subsequently in Cohort 2 and the overall stratum. Additional clinically important benefits demonstrated by betrixaban 80 mg include significant reductions in: (a) symptomatic VTE; (b) ischemic stroke; (c) fatal or irreversible outcomes; (d) VTE-related mortality; and (e) VTE-related re-hospitalization. Importantly, there was no increase in major bleeding and fewer occurrences of intracranial haemorrhage compared with the standard of care. The 1.8 times increase in CRNM bleeding is clearly outweighed by the lack of increase in major bleeding and the absolute efficacy benefit, in particular by the reduction in life-threatening VTE events including VTE-related rehospitalisation and VTE-related death. Increased CRNMB has not prohibited the approval of anticoagulants previously, even for chronic use indications. CRNMB events on betrixaban were primarily mild to moderate in severity, the majority did not require specific treatment, and few required hospitalisation. Thus, a favourable benefit-risk profile exists for betrixaban in both the overall (80/40 mg) population and in the 80 mg stratum alone

Summary of the Applicant's position:

a. Benefit-risk for APEX population (80/40 mg)

The efficacy profile for the combined 80 and 40 mg betrixaban population was described above and demonstrated statistically significant reductions not only in the primary composite outcome, but also for symptomatic VTE including VTE-related death, VTE-related hospitalisations and ischemic stroke.

Over the course of a median 36 days of treatment with betrixaban, there was no evidence of an increase in major bleeding compared with enoxaparin administered for a median of 9 days, (RR = 1.19, p = 0.554). In a trial of > 7,500 subjects, this is unlikely to be a chance finding. With respect to individual major bleeding types, more GI bleeding events occurred on betrixaban (as has been observed with other FXa inhibitors) but fewer intracranial haemorrhages (as also has been observed with other FXa inhibitors) (**Table 55**).

Although CRNM bleeding occurred more frequently during extended duration betrixaban than during standard duration enoxaparin (RR = 2.3; p < 0.001), the majority of these events were mild (42.6%) to moderate (44.2%) in severity, only 12% required hospitalisation. Similarly, CRNM bleedings classified as SAEs were mostly mild (26.2%) to moderate (57.0%) in severity, 49.5% did not require any treatment and 67.8% did not require or prolong hospitalisation. The two arms showed similar severity, duration, actions taken with study drug, and rates of hospitalization.

Table 50. Adjudicated major bleedings through 7 days after the last dose of study drug by anatomic location by treatment group (safety population)

	Betrixaban (N=3,716)	Enoxaparin (N=3,716)
Major Bleeding Rate	25 (0.67)	21 (0.57)
Bleeding Site		
Gastrointestinal	19 (0.51)	9 (0.24)
Gastrointestinal Upper	18 (0.48)	7 (0.19)
Gastrointestinal Lower	1 (0.03)	2 (0.05)
Intracranial	2 (0.05)	7 (0.19)
Intraocular	0	1 (0.03)
Pericardial	1 (0.03)	1 (0.03)
Hematoma	1 (0.03)	1 (0.03)
Epistaxis	1 (0.03)	0
Bleeding associated with non-cardiac surgery	0	1 (0.03)
Rectal	1 (0.03)	1 (0.03)

Individual studies with DOACs have shown differences in bleeding reductions depending on whether major bleeding or CRNMB is considered. Meta-analyses have confirmed that DOACs are associated with greater reductions in major bleeding compared with reductions in CRNMB.

It appears that DOAC therapy may result in less "tissue" bleeding (brain, retroperitoneal, serosal, joint and muscular) classified as major bleeding but more "tube" (epithelial) bleeding (genitourinary tract, gastrointestinal, respiratory) more often classified as CRNM bleeding and generally more manageable than tissue bleeding. This hypothesis may underlie the similar rates of major bleeding but higher rates of CRNMB on betrixaban in APEX.

In clinical practice, CRNM bleeding events can be readily managed as they were during the conduct of APEX. The 35 day follow-up post hospital discharge in APEX is consistent with standard clinical follow-up in real world clinical practice. The overall increased bleeding frequency should be considered acceptable with no observed differences between betrixaban and enoxaparin for major, fatal, or intracranial bleeding. CRNM bleeding rates in APEX are within the acceptable levels across the DOAC class for other indications, including their ratio to major bleeding, and in fact are lower by comparison (**Figure 22**, and **23**).

Figure 20. Absolute Major Bleeding Risk for Betrixaban in APEX Compared to Other Approved DOACs

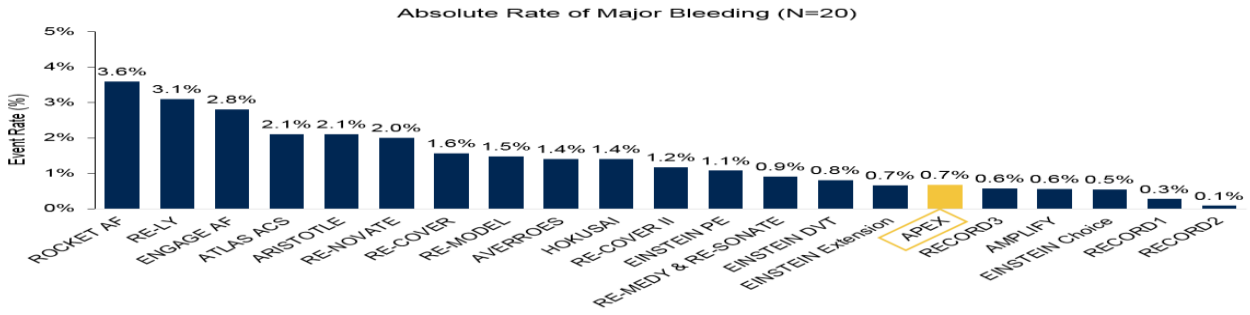
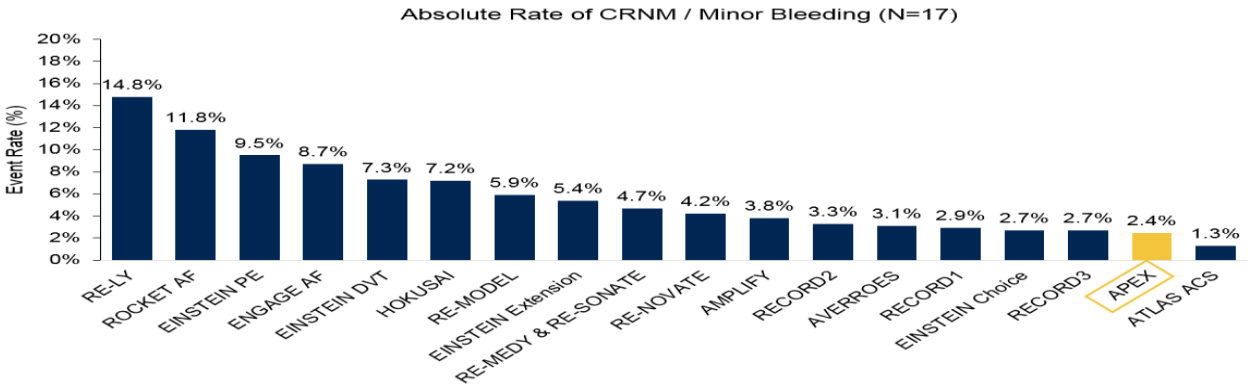


Figure 21. Absolute CRNM or Minor Bleeding Risk for Betrixaban in APEX Compared to Other Approved DOACs



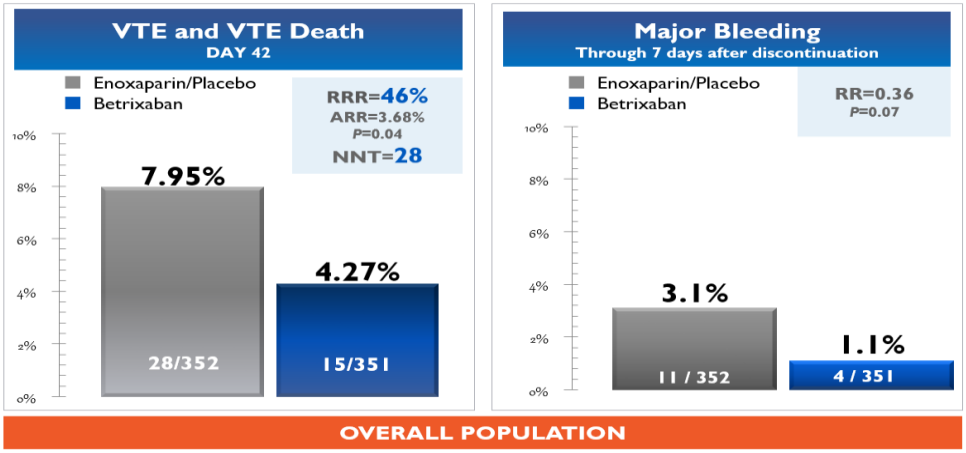
The annual number of excess hospitalisations expected across the EU extrapolated from APEX for CRNM bleeding (5,000) is just a fraction of the 35,000 rehospitalisations and deaths due to VTE. Labelling, education, and physician familiarity with the FXa inhibitor class (used in the majority of indications at even higher equivalent doses and for longer duration than betrixaban) are expected to minimize bleeding risk and ensure appropriate management of these bleeding events.

In the applicant's opinion, the excess in CRNM bleeding on betrixaban does not outweigh the clinical significance and the positive benefit from reductions in VTE, VTE-related death, and VTE-related hospitalization compared with enoxaparin. Further considering the absence of an increase in major bleeding, the benefit-risk for betrixaban in the total population is clearly favourable.

One particular high-risk APEX subgroup, those admitted to intensive care units, highlights the favourable benefit-risk of betrixaban. The composite efficacy rate was 7.95% on enoxaparin and 4.27% on betrixaban (RRR = 0.46; ARR = 3.68%; p = 0.04; NNT = 28). In this setting, the substantial efficacy advantage of betrixaban did not result in an increase in major bleeding.

In fact there were numerically fewer major bleeding events on betrixaban (3.1% on enoxaparin, 1.1% on betrixaban; p = 0.07) (**Figure 24**).

Figure 22. Analysis of Primary Efficacy Endpoint and Major Bleeding for Patients with ICU Stays, mITT Population



Source: Chi, G., et al. (2018). Efficacy and Safety of Betrixaban Versus Enoxaparin for Venous Thromboembolism Prophylaxis in Critically Ill Patients: An APEX Trial Substudy. Manuscript submitted for publication.

b. Benefit-risk in 80 mg stratum

Following CHMP guidance to identify a target population with a more favourable benefit risk profile than was observed in the overall study, the applicant excluded patients with severe renal impairment (CrCL < 30 mL/min) and those receiving concomitant potent P-gp inhibitors. Both of these groups of

patient had been treated with a 50% lower betrixaban dose and a lower enoxaparin dose. The former, because they were considered to represent an especially vulnerable subgroup at elevated risk for bleeding> The latter because it was known that betrixaban elimination was mediated in part by P-gp transporters and that potent inhibitors of P-gp might increase betrixaban concentrations. In retrospect and based on outcomes in the 40 mg stratum, the applicant considers that the 40 mg dose may be lower than optimal for patients in that stratum and as a consequence these patients did not appear to derive a positive benefit-risk profile compared to standard duration enoxaparin. Removing the 40 mg stratum leaves the 80 mg stratum as a target population with a more favourable benefit-risk than in the total study population.

Following the hierarchical testing scheme for the primary efficacy endpoint in the 80 mg stratum (excluding patient X), starting with Cohort 1, followed by Cohort 2 and then the overall PEOP population, yields successive positive outcomes (**Table 56**).

Table 51. Primary Efficacy Endpoint in the 80 mg Stratum (excluding Patient X) by Cohort, PEOP

Population	Betrixaban n/N (%)	Enoxaparin n/N (%)	RR (95% CI)	ARR (95% CI)	RRR (95% CI)	p-Value	NNT
Cohort 1	92/1,464 6.28 (5.04, 7.53)	128/1,521 8.42 (7.02, 9.81)	0.75 (0.58, 0.97)	2.13 (0.26, 4.00)	0.253 (0.033, 0.423)	0.026	47
Cohort 2	115/2,213 5.20 (4.27, 6.12)	162/2,289 7.08 (6.03, 8.13)	0.74 (0.59, 0.94)	1.88 (0.48, 3.28)	0.258 (0.065, 0.411)	0.011	54
Overall	120/2,426 4.95 (4.08, 5.81)	180/2,511 7.17 (6.16, 8.18)	0.70 (0.56, 0.87)	2.22 (0.89, 3.55)	0.303 (0.128, 0.443)	0.001	46

This efficacy advantage in the 80 mg stratum was achieved without an increase in major bleeding (**Table 57**) and with a low absolute major bleeding rate on betrixaban . The observed 2-fold increase in CRNM bleeding (compared to a 2.3-fold increase in the total study population) should be considered in the context of a 4-fold longer treatment duration with betrixaban (median 36 days) compared to enoxaparin (median 9 days) followed by placebo. Notably, there were fewer ICH events on betrixaban 80 mg which enhances the favourable benefit-risk profile in this stratum.

Table 52. Adjudicated Major, CRNM, ICH Bleeding Events through 7 Days after Discontinuation of All Study Medication, 80 mg Dose Received, Safety Population

Bleeding Type	Betrixaban n/N % (95% CI) [1]	Enoxaparin n/N % (95% CI) [1]	Relative Risk (95% CI) [2]	p-Value [3]	ARR (95% CI) [4]	NNH [5]
Major Bleed	15/2,986 0.50 (0.25, 0.76)	16/2,991 0.53 (0.27, 0.80)	0.939 (0.465, 1.896)	0.861	0.03 (-0.33, 0.40)	3,334 NS
CRNM Bleed	66/2986 2.21 (1.68, 2.74)	33/2991 1.10 (0.73, 1.48)	2.00 (1.32, 3.03)	< 0.001	-1.11 (-1.75, -0.46)	91
ICH Bleed	1/2986 0.03 (0.00, 0.10)	7/2991 0.23 (0.06, 0.41)	0.143 (0.018, 1.162)	0.070	0.070	500

Further support for the 80 mg stratum is provided by statistically significant time-to-event analyses summarized in the forest plot of hazard ratio and 95% CI for symptomatic VTE including VTE-related death, VTE-related rehospitalisation, ischemic stroke, all fatal or irreversible events, and VTE-related mortality.

Overall these efficacy and safety findings represent a more favourable benefit-risk profile than was observed in the total study population.

Extrapolating these important clinical outcomes to the real world set of similar risk patients in the EU (~4.7 million) yields the following projected impact on public health on an annual basis: ~79,900 fewer asymptomatic events, ~42,770 fewer symptomatic events, ~12,690 VTE-related deaths, ~37,130 fewer VTE-related re-hospitalisations, and only 1,410 additional bleeding hospitalisations.

Ground #4: Learnings from prior VTE prophylaxis trials and its precedent

- CHMP described in its negative trend vote that the reduction in VTE without an increase in major bleeding in favour of betrixaban in APEX could be the result of a play of chance. This should not be the case for two reasons. First the sample size of 7,513 patients is well representative of the proposed indication. Secondly, betrixaban's demonstrated positive benefit risk, in an indication where other agents in the class have failed, is consistent with precedent in the field that showed that patient selection, dose selection, and pharmacologic properties can distinguish individual antithrombotics and their demonstrated safety and efficacy within the same class or across a class of drugs and within the same indication. The 80 mg betrixaban dose in APEX was carefully derived by targeting a magnitude of thrombin generation inhibition intermediate between rivaroxaban 10 mg QD (a Factor Xa inhibitor with excess bleeding in medical patients) and apixaban 2.5 mg BID (a Factor Xa inhibitor with insufficient efficacy in medical patients).

  CHMP suggested that the bar is higher for betrixaban in extended VTE prophylaxis because other agents in the class failed to demonstrate positive benefit risk. In our view, the success of betrixaban in demonstrating a reduction in VTE without an increase in major bleeding is because of its unique drug properties (~24 hr half-life resulting in low peak-trough concentration ratio when dosed once-daily, low renal clearance, absence of CYP3A4 drug interactions) and the selection of an enriched high-risk population. There is precedent for success and CHMP approval for a member of a drug class when others have not demonstrated a positive benefit risk : (a) in Acute Coronary Syndrome (ACS), the factor Xa inhibitor rivaroxaban was approved based on a demonstrated benefit in the reduction of myocardial infarction but apixaban failed to demonstrate efficacy with worse bleeding outcomes and dabigatran had excess bleeding and a concern regarding excess myocardial infarction; and (b) in the setting of Percutaneous Coronary Intervention (PCI), the gpIIb-IIIa antagonists eptifibitide and abciximab demonstrated a reduction in myocardial infarction and were approved for this indication whereas tirofiban did not demonstrate efficacy and was not approved. Finally, (c) in moderate risk hospitalized medically ill patients, short 6 to 14 day duration enoxaparin demonstrated a reduction in

  VTE without an increase in major bleeding versus placebo and was EMA approved whereas dalteparin failed to demonstrate a positive benefit risk and was not approved for this indication.

Summary of the Applicant's position:

The applicant considered that specific learnings from the past failed attempts in this therapeutic are led to the selectin of the right molecular target, posology, and at-risk target population that yielded successful outcomes across multiple efficacy parameters in APEX without an increase in major bleeding, as described in our hypothesis.

Three prior trials have been conducted in extended VTE prophylaxis versus standard duration enoxaparin for acutely ill medical patients (**Table 58**).

Table 53. Anticoagulants Studied for Prevention of VTE in Acutely Ill Medical Patients

Anticoagulant	**Enoxaparin**	**Apixaban**	**Rivaroxaban**	**Betrixaban**	
Half-life (hrs)	5–7	12	5–9	19–27	
Study	EXCLAIM	ADOPT	MAGELLAN	APEX	
Dose	40 QD	2.5 BID	10 QD	80 QD	80/40 QD
		efficacy			
NOAC Efficacy (%)	2.5 *	2.71	4.4	4.95	5.3
Enoxaparin Efficacy (%)	4.0	3.06	5.7	7.11	7.03
RR	0.62	0.87	0.77	0.69	0.76
p-value	<0.04	0.44	0.002	0.002	0.006
		safety			
NOAC Major Bleeding (%)	0.8	0.47	0.6	0.50	0.67
Enoxaparin Major Bleeding (%)	0.3	0.19	0.3	0.53	0.57
RR	2.51	2.58	2.2	0.94	1.19
p-value	<0.05	0.04	0.03	0.861	0.554

In moderate risk populations, in EXCLAIM with extended duration enoxaparin 40 mg QD and in MAGELLAN with extended duration rivaroxaban 10 mg QD, superior efficacy was demonstrated but associated with a > 2-fold increase in major bleeding rendering the benefit-risk unfavourable. In a lower risk population, extended duration apixaban 2.5 BID in ADOPT failed to achieve superior efficacy and was associated with a >2-fold increase in major bleeding. Although none of these trials showed a net benefit of extended VTE prophylaxis, they all demonstrated a persistent rate of VTE beyond the standard prophylaxis duration and confirmed the unmet need for a better therapy for extended duration prophylaxis.

The range of negative and positive results from extended VTE prevention studies is consistent with historical antithrombotic trials in other indications that showed that patient selection, dose selection and pharmacologic properties can distinguish individual antithrombotics within the same class or across a class of drugs and within the same indication. In ACS, rivaroxaban demonstrated statistically significant benefit but apixaban failed to demonstrate efficacy with worse bleeding outcomes and dabigatran had excess bleeding and a concern regarding excess myocardial infarction. In the setting of Percutaneous Coronary Intervention (PCI), the gpIIb-IIIa antagonists eptifibitide and abciximab demonstrated a reduction in myocardial infarction and were approved for this indication whereas tirofiban did not demonstrate efficacy and was not approved. In moderate risk hospitalized medically ill patients, short 6 - 14 day duration enoxaparin demonstrated a reduction in VTE without an increase in major bleeding versus placebo and EMA approved whereas dalteparin failed to demonstrate a positive benefit risk and was not approved for this indication.

Therefore, the failure of enoxaparin, rivaroxaban, and apixaban in extended VTE prophylaxis should not be used to pre-judge the performance of betrixaban in APEX. In fact, learnings from these prior trials informed our selection of the right drug, the right dose and the right patients in APEX which produced strong efficacy and acceptable safety outcomes.

Ground #5: Biological plausibility in VTE prophylaxis

- In its negative trend vote CHMP suggested that there is not biological plausibility for the efficacy of betrixaban in the proposed indication. The Applicant refutes that claim based on evidence. Biological plausibility and precedence for the efficacy of VTE prophylaxis anticoagulation in acutely ill medical patients without an increase in major bleeding compared to placebo was first established in trials of short duration LMWH (for 6-14 days). These early trials also demonstrated that there is a high risk of VTE beyond 6 to 14 days. The persistence biological plausibility for VTE risk beyond hospitalisation for a total of 35 to 42 days and the potential of anticoagulants to reduce the rate of these events was confirmed in two extended VTE DOAC studies. In these studies biological plausibility was again demonstrated in acute medically ill patients, this time showing that VTE events persist beyond short duration anticoagulation prophylaxis and that these events can be modified by in-hospital and extended duration anticoagulation. However, due to variable event rates and efficacy and an increase in major bleeding a positive benefit-risk profile was not demonstrated. The unique pharmacologic properties of betrixaban (its 24 hour half-life resulting in low peak to trough concentrations when dosed once-daily, low renal clearance, and with a lack of drug-drug interaction with agents metabolized by CYP3A4 coupled with the large APEX study population which was enriched for higher VTE risk, underlies the biological plausibility of betrixaban to improve efficacy results while not increasing major bleeding. Also the APEX results in the D-dimer subpopulation (as measured by central lab) are nearly identical to and prospectively validate what was observed previously in the MAGELLAN trial (rivaroxaban) D-dimer subpopulation.

Summary of the Applicant's position:

As noted above, three large randomized studies established the biological plausibility and proof of concept for extended VTE prophylaxis in acute medically ill patients – EXCLAIM (enoxaparin), ADOPT (apixaban), and MAGELLAN (rivaroxaban). Each of these studies showed that VTE events continue to occur after standard LMWH prophylaxis and that extended duration anticoagulation can reduce the frequency of these events. The major drawback in these studies was an increase in ISTH major bleeding that offset the clinical benefit. Each of the prior trials had potential flaws in either the study design or dose selection that likely undermined the outcomes. Our data show that betrixaban can reduce VTE (including VTE-related death) with a larger treatment effect than shown with other anticoagulants in this population and without an associated increase in major bleeding. Moreover, this positive benefit-risk is largely attributable to betrixaban's unique pharmacologic properties and inclusion of a study population at high risk for VTE as well as lessons from prior studies related to enrichment and dosing.

In developing betrixaban, the sponsor has attempted to optimize not only the drug properties but also the patient population in which it was to be studied. With respect to the choice of drug target, Factor Xa is a proven anticoagulant mechanism across both venous and arterial thrombotic disorders. Although of the FXa inhibitors as a class have similar potencies, betrixaban distinguishes itself from the other compounds, particularly at the level of the pharmacokinetic properties. Betrixaban has an effective half-life of 19 to 27 hours and, as a consequence, has a low peak-totrough concentration ratio when dosed once-daily.

Betrixaban's pharmacokinetic profile is well-suited for elderly high-risk medical patients (once-daily dosing, low peak-trough fluctuation in plasma concentration, low renal clearance, and no CYP3A4 interactions). The 80 mg dose of betrixaban was carefully derived by targeting a magnitude of thrombin generation inhibition intermediate between rivaroxaban 10 mg QD (a Factor Xa inhibitor with excess bleeding in medical patients) and apixaban 2.5 mg BID (a Factor Xa inhibitor with insufficient efficacy in medical patients). Furthermore, APEX population pharmacokinetic analyses confirmed that betrixaban 80 mg once-daily concentrations result in thrombin generation levels corresponding to INR values of 1.9 to 2.3.

In principle, a low peak-to-trough concentration ratio should provide the lowest risk of exaggerated pharmacologic toxicity (i.e., bleeding). The peak-to-trough ratios of anti-FXa activity in a study comparing apixaban and rivaroxaban were 4.7-fold and 16.5-fold for apixaban and rivaroxaban, respectively. In contrast the peak-to-trough for betrixaban was 2.6-fold (Study 15-507). These higher peak-to-trough ratios of anticoagulation for apixaban and rivaroxaban are associated with higher rates of bleeding relative to the comparator in their extended VTE prophylaxis studies, ADOPT and MAGELLAN, than was seen for betrixaban in APEX.

Table 54. Comparison of peak-to trough plasma concentrations and Anti-FXa activity peak to trough ratios for VTE prevention dose in healthy subjects

Compound	Dose	Geometric Mean C_{max_ss} (ng/mL)	Geometric Mean C_{min_ss} (ng/mL)	Anti-FXa Activity Peak/Trough Ratio *	Source
Apixaban	2.5 mg BID	81	17	4,7	Frost et al., 2014
Rivaroxaban	10 mg QD	171	10	16.5	Frost et al., 2014
Betrixaban	80 mg QD	33.6	8	2.6	Study 15-507

* Different standards units used for betrixaban anti-FXa activity assay than apixaban and rivaroxaban so only ratios can be compared.

In APEX, high risk acute medically ill patients were enrolled based on their underlying disease and substantial immobility. If one uses either the efficacy event rate or the major bleeding rate in the enoxaparin control arm as a surrogate for risk, the rates of these events in the control arm of APEX were higher than the rates of the other studies, which implies that APEX enrolled the highest risk population of the four trials. Furthermore, the population in APEX was considerably older than in the other studies (APEX mean age 76.4 years, 68% ≥ 75 years; EXCLAIM mean age 68 years, 30% ≥ 75 years; MAGELLAN median age 71 years, 39% ≥ 75 years; ADOPT mean age 67 years, 30% ≥ 75 years) and the proportion of severely immobilised was highest in APEX (97% in APEX; 42% in EXCLAIM, not published for MAGELLAN; 29% in ADOPT). Confirmation of the importance of immobility is provided by the highest risk APEX patients, those in intensive care units, for whom absolute event rates are high and the betrixaban benefits appear larger (ARR of 3.68%, NNT=28) and without an increase in major bleeding (Appendix Figure A.17).

The MAGELLAN study also demonstrated a reduction in VTE events in patients who were D-dimer positive on central laboratory testing (RRR = 29.0% [8.0, 46.0], p < 0.001) (Appendix Figure A.18). The results of the subsequent APEX study in patients who were D-dimer positive on central laboratory testing (RRR = 29.5% [11.6, 43.9], p = 0.002) are nearly identical to those of the MAGELLAN study in patients who were D-dimer positive on entry.

Thus, the hypothesis that extended duration Factor Xa inhibition can improve upon the current standard of therapy appears to be validated in two studies.

The 80 mg betrixaban dose also had supportive outcomes, similar to those on warfarin, in an arm of the Phase 2 EXPLORE-Xa study of stroke prevention in atrial fibrillation. In this study (N=127/arm; median follow-up = 150 days) on betrixaban 80 mg once-daily there were 1 ischemic stroke, no deaths, 3 major, and 2 CRNM bleeding events and on warfarin there were no strokes, 1 vascular death, 5 major, and 4 CRNM bleeding events.

The favourable benefit-risk profile established for extended VTE prophylaxis with betrixaban was critically dependent on the selection of a higher risk patient population, refined dose selection, and use of an agent with improved pharmacologic properties, all learnings from decades of prior trials in acutely ill medical patients that enabled success where prior trials had failed.

Report from the SAG

It is acknowledged that there is an unmet medical need for a prolonged treatment with anticoagulants in acutely ill medical patients at increased risk for thromboembolic events. More than 50% of non-fatal VTE events and VTE related deaths in these patients occur following discontinuation of standard duration prophylaxis.

Following a request from the applicant at the time of the re-examination of the CHMP opinion concerning the use of Dexxience for the prophylaxis of VTE in adults hospitalised for an acute medical illness, the CHMP has convened a Scientific Advisory Group (SAG) to discuss the following issues.

The SAG was invited to provide their views on the CHMP grounds for refusal, taking into account the applicant's response:

- The efficacy of Dexxience in the proposed indication has not been robustly demonstrated. Evidence presented was based on a single pivotal study in which the first step of the statistical testing (according to the pre-specified closed testing gate keeping procedure) of the primary endpoint did not yield a reliable result of compelling evidence of a true difference between the treatment groups. There is further uncertainty around the reliability of the results due to missing data.
- Treatment with Dexxience was associated with an increased risk of bleeding events (major or clinically relevant non major bleedings) compared to the comparator in the trial (both at 14 days in comparison to enoxaparin and at the end of the trial). This is a serious concern considering that the target population comprises patients with comorbidities for which potential bleedings may have serious consequences. This is further compounded by the pharmacokinetic properties of Dexxience, which could have significant implications for the occurrence and management of such events in clinical practice.

In addition to providing their views on the CHMP grounds for refusal, the experts wereinvited to provide input on the following questions:

1. **Please discuss the clinical relevance of the magnitude of the treatment effect of Betrixaban as documented in the APEX study (primary and secondary endpoints), in particular in terms of absolute risk reduction, and the strength of the evidence, taking also into account the results on other clinical trials in similar settings, i.e. the ADOPT trial (long term Apixaban vs. short term Enoxaparin, N Engl J Med 2011; 365: 2167-77), the MAGELLAN trial (long term rivaroxaban vs. short term Enoxaparin, N Engl J Med 2013; 368: 513-523), and the EXCLAIM study (long term Enoxaparin vs. short term Enoxaparin, Ann Intern Med. 2010; 153: 8-18).**

The Group considered that there are important limitations in the APEX study which do not allow drawing conclusions on the clinical relevance of the reported results in the study. The pre-specified analysis of the study failed to return compelling results of statistical significance for betrixaban. Considering that unlike other Factor Xa inhibitors which have been investiagted in previous clinical trials there is no prior experience with betrixaban, therefore the result of the APEX study are not considered sufficient to robustly demonstrate the effectiveness of betrixaban in the claimed indication.

In addition, the Group noted that due to the way that subjects were recruited in the study, with an emphasis of baseline D-dimers levels, it is not possible to identify the patients that could potentially benefit from extended thromboprophylaxis. The Group advised that the levels of D-dimers is not a specific marker to identify patients at high risk of thromboembolic events but rather identify a goup with a general non-specific risk of co-morbidities and mortality. Furthermore, the Group considered that the patients investigated in the APEX study do not necessarily reflect the frailest patients at highest risk. In real life these patients are typically older, present with multiple co-morbidities or commonly receive concomitant medications such as clarithromycin which is proposed as a contraindication of use. These discrepancies between the studied population and the real life setting patients make it more difficult to establish the clinical relevance of the use of betrixaban in the prophylaxis of venous thromboembolism.

2. **Please discuss the importance of the increased risk of "clinically relevant non major bleedings" associated with Betrixaban treatment in the studied population and in clinical practice.**

    - **Are differences expected concerning severity, consequences and handling of bleedings in clinical practice compared to patients included in the clinical study?**
    - **How would such differences affect the clinical utility of the drug?**
    - **Do you consider the proposed risk minimization measures effective and workable to adequately minimize the bleeding risk in clinical practice? Could you think of (additional) measures to protect patients from the risk of clinically relevant bleeding?**

The Group expressed their concerns about the reported "clinically relevant non major bleedings" associated with betrixaban treatment. The Group advised that in clinical practice there are a number of reasons why detrimental differences could be expected compared to the events reported in the APEX study. As generally in real life, patients are not followed up with the same rigour of a clinical trial. Therefore, bleeding events in real-life could have more serious sequelae than in the APEX study. The pharmacokinetic properties of betrixaban were highlighted by the Group as an additional complication in managing these risks in clinical practice. As these differ markedly compared to other factor Xa inhibitors there is no experience in how to minimise bleeding events if they were to occur. In addition, the Group expressed their concerns over the food effect with betrixaban, as in the intented frail target population it can be expected that patients experiencing a bleed may neglect their food intake that could further exacerbate these type of events. Conversely, there is the possibility that patients experiencing bleeding events, may elect to discontinue treatment that could potentially put them at a risk of a thrombotic event.

Based on the above, the Group considered that there are important limitations in the clinical utility of the drug. The Group could not provide any additional recommendations on how to

minimise the risk of bleedings with betrixaban which could be further attenuated by concomitant use of commonly used medications such as anti-platelet drugs or SSRIs.

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the Scientific Advisory Group.

Ground #1-Clinical burden

The CHMP agreed that there is a medical burden associated with the thromboembolic risk in AMI patients and that there is an unmet medical need for a prolonged treatment beyond about 10 days with an established positive benefit/risk balance (see also Section 2.1.2 of this report).

The SAG that had been convened by the CHMP during this procedure also confirmed this (see Additional expert consultation, under Section 2.5.3)

However, the CHMP considered that data available do not allow concluding on a mortality benefit in these patients by a prolonged administration of betrixaban.

The Applicant provided data on a correlation between asymptomatic proximal DVTs in medically ill patients and mortality from the literature and from the APEX trial. Thereby, the Applicant suggested that a reduction in proximal DVTs by betrixaban may considerably reduce mortality. This assumption is not shared:

The correlation between proximal asymptomatic DVT and mortality that was described in the post hoc Analysis of Vaitkus, et al., 2005 does not indicate a causal relationship between DVT and death. Medically ill patients were included in the analysis. Among the medical conditions were congestive heart failure in about 60% of the patients, respiratory failure in 34 – 39%, and cancer in 4 – 6%. Reasons for death in the proximal DVT group were vascular death (n=4; 36.4%), cancer related (n=3; 27.3%) and other causes of death (n=4; 36.4%). None of the deaths in this group was considered as likely VTE related.

The authors concluded: "The association between proximal DVT and subsequent mortality does not necessarily establish causality.… Plausible explanations include that the proximal DVT's directly contributed to increased mortality via their propensity to embolize or, alternatively, that developing a DVT is a marker for severe underlying illness."

The same considerations hold true for the APEX trial and the association between time to all-cause mortality after ultrasound in patients without a symptomatic VTE at Visit 3 that was shown by the Applicant. The APEX trial did not show a mortality benefit of prolonged betrixaban treatment:

VTE related death as an efficacy outcome through Visit 3 (**Table 31** in this report) was

- in Cohort 1 (Primary efficacy outcome population, PEOP), Betrixaban vs. Placebo: 12 (0.6%) vs. 11 (0.6%)

- in all patients in the mITT population (First Secondary Efficacy Outcome Population, FSEOP): 13 (0.6%) vs. 17 (0.6%). Non-VTE related death was 134 (3.6) vs. 137 (3.7) in this group.

In the safety analysis, a total of 437 deaths were recorded in APEX: 213 patients in the betrixaban group vs. 214 patients in the enoxaparin group. In addition, 10 patients who received no active drug died corresponding to mortality rates of 6% in each treatment group. There was no relevant difference in all-cause mortality between the groups.

When analysing CEC adjudicated all deaths occurring up to Day 77, cause of death was adjudicated for 425 of the 437 patients.

The most frequent adjudicated causes of death were: cardiovascular due to heart failure/cardiogenic shock (40 betrixaban patients [19%] vs. 56 enoxaparin patients [26%]); non-cardiovascular due to infection (44 betrixaban patients [21%] vs. 37 enoxaparin patients [17%]); non cardiovascular due to pulmonary causes (28 betrixaban patients [13%] vs. 24 enoxaparin patients [11%]); and other cardiovascular due to ischaemic stroke (including patients who died due to an ischaemic stroke which occurred prior to entry into the study) (24 betrixaban patients [11%] vs. 28 enoxaparin patients [13%]). The incidences of deaths adjudicated as VTE-related were 0.4% in the betrixaban group and 0.7% among the enoxaparin treated patients.

It cannot be entirely excluded that in some of the patients that died e.g. due to heart failure/cardiogenic shock, undetected thromboembolic events may have played a role. However, it becomes clear that mortality in most of these patients was not related to thromboembolic events during the observation period in the APEX trial.

In summary, whilst it is agreed that there is a medical burden associated with the thromboembolic risk in AMI patients and that there is an unmet medical need for a prolonged treatment with an established positive benefit/risk balance, this does not change the conclusions on the benefit risk balance of prolonged treatment with betrixaban in the patient population investigated in APEX.

The results of the APEX trial did not indicate an overall mortality benefit in patients treated with betrixaban (prolonged) vs. enoxaparin (short term). Most of the deaths observed in this patient population were not related to thromboembolic events. Therefore it cannot be concluded that a reduction in asymptomatic DVTs does translate into a mortality benefit in the patient population included in the APEX trial.

Ground #2- APEX results

The CHMP re-iterated that the question whether Patient X should be included in the primary analysis is not a key issue in the evaluation of this application, as the p value of 0.054 or 0.048, does not change the robustness of efficacy results of a study in an application based on one pivotal trial.

In addition, the CHMP concluded that according to the pre-specified SAP, patient X did not suffer an outcome event since the symptomatic event occurred after Visit 3. The CHMP noted the definition of the primary endpoint as detailed in the SAP, according to which symptomatic events are included up to Visit 3 (or Day 42 if Visit 3 has not occurred by then).

Moreover the CHMP noted that the SAP of the APEX study states ""If an asymptomatic event is detected on the same day as, or within two days after, onset of a symptomatic DVT, only the symptomatic DVT will be included in analyses as an event." Therefore, whether an event was symptomatic or not, did not rely on the definition of the Primary Endpoint window. Thus, the event that occurred to Patient X on Day 38 was a symptomatic event that occurred after Visit 3.

Importantly, the CHMP noted that the EC decision occurred after database lock. The ARO was not responsible for the study and did not have a role as sponsor. Therefore their interpretation of the data has no priority over the original CRO conclusion.

As detailed in the initial evaluation by the CHMP, the robustness of the results was further explored by applying multiple imputation analyses. This is important since there was an imbalance in the overall rate of protocol deviations (betrixaban 833 (22.2%) vs. enoxaparin 742 (19.8%)) which was mainly related to a difference in missing or not appropriately performed Compression Ultrasound Sonography (CUS) in patients without an adjudicated symptomatic event (514 (13.7%) vs. 450 (12.0%)); 16.4% in the betrixaban arm and 14.7% in the enoxaparin arm were excluded from the PEOP for missing CUS.

Overall the analysis with imputation based on the missing-at-random assumption yielded a result that was similar to the primary analysis without imputation (cohort 1: p=0.11, cohort 2: p=0.042, cohort 3: 0.008), whereas in the jump-to-reference analysis the treatment effect was smaller (cohort 1: p=0.219, cohort 2: p=0.099, cohort 3: p=0.027). These analyses showed that assumptions about efficacy for missing data were relevant for the statistical significance in Cohort 1. As discussed above, proximal DVTs may be an indicator of severe disease and mortality risk. It is among the possibilities that the imbalance in missing ultrasound data is due to more patients in the betrixaban group not showing up due to severity of the disease. Such patients have a higher likelihood for asymptomatic DVTs. Therefore, it cannot be assumed a priori that the imbalance in missing ultrasound data had no effect on the overall outcome.

Additional sensitivity analyses based on the mITT analysis population were explored during the application procedure for a marketing authorization also indicating that the primary endpoint results in Cohort 1 were not statistically robust.

The key analysis to be considered is the analysis in Cohort 1. The primary efficacy outcome asymptomatic proximal DVT (as detected by ultrasound), Symptomatic DVT (proximal or distal), Non-fatal PE, or VTE-related death was largely consistent with current EMA guidelines. All-cause mortality instead of VTE-related death was included in a secondary efficacy endpoint. The event rate (95% CI) for this secondary efficacy outcome in Cohort 1 was 11.5 (10.1-12.9) % for betrixaban and 12.9 (11.4-14.3) % for the comparator enoxaparin (nominal p-value=0.164) respectively. The event rate (95% CI) % for this secondary endpoint in the overall population was 9.2 (8.2-10.2) % and 10.9 (9.8-11.9) % (nominal p-value=0.024) respectively.

The magnitude of the estimate of reduction in primary endpoint events in the APEX trial could be considered clinically relevant when disregarding the uncertainties concerning the robustness of the results and the definition of the appropriate target population.

Regarding the statistical analysis, the CHMP noted that the issue had been discussed during the Scientific Advice procedure and the Applicant had been warned about the risk of pursuing their selected strategy.

This assumed that patients with elevated D-dimer levels would have greater VTE risk and a more favourable B/R profile than the overall AMI population. To investigate this hypothesis, the study population was enriched with for these patients by amendment 3 dated 04 June 2014, at a time when approximately, half of the study population had already been enrolled. After this amendment, only patients with baseline D-dimer $\geq$ 2x ULN and/or age $\geq$ 75 years (union) and with a modified risk pattern were included, enrolment of patients in the biomarker negative subgroup (age <75 and D-dimer <2x ULN) was ceased and the statistical analysis plan was amended accordingly. So in fact, patients with increased D-dimer levels were intentionally predefined as the primary population to be investigated. It was not just a subgroup intended to assess robustness of overall results.

Predefining the statistical gating analysis therefore represented a pre-study assumption about a patient population with a positive B/R in an area with three previously failed studies in the overall AMI population. It was the aim of the trial to investigate a patient population that was different from the population included in the above mentioned three failed trials. A single pivotal study in a broad population similar to ADOPT, MAGELLAN and EXCLAIM appeared not likely to be successful beforehand. However, the key hypothesis of the study was not confirmed.

Considering that 3 previous studies in the same broad AMI population did not show a positive B/R for prolonged treatment with either enoxaparin or 2 DOACs, one borderline positive study with another DOAC, i.e. betrixaban, in an at least partially overlapping patient population is not sufficient to establish a new treatment paradigm. Post hoc statistical measures to formally rescue a borderline positive (and therefore statistically not compelling) result in the fourth study are not appropriate. Additional confirmation is required for a change of the overall treatment concept.

The requirements for one pivotal trial as outlined in CPMP/EWP/2330/99 have therefore to be applied to the first step of the primary analysis (Cohort 1). A change in the statistical approach post hoc cannot be considered, esp. not in this situation with 3 failed previous studies. Additional confirmation, i.e. by a second study is considered necessary.

This is even more the case since issues like selection bias and difference in patient handling and control in clinical practice may shift the B/R balance. E.g. analysis of D-dimer levels was a prerequisite in the study. As this is not standard in clinical practice, it is not entirely clear whether this criterion by itself was a selection criterion.

- As outlined above, an association between asymptomatic proximal DVT and mortality does not necessarily imply causal relationship. Development of asymptomatic DVTs may in many cases just be an indicator of severe underlying disease leading to death.

- A reduction in ischemic strokes in patients with heart failure or ischemic stroke at entry with some exceptions is not due to VTE. An analysis of whether these patients were at appropriate baseline therapy e.g. for atrial fibrillation is out of the scope of this procedure. Similarly, the time to event analysis for all fatal or irreversible events includes events that are relevant for the patients but are not necessarily related to DVT and VTE (e.g. ischemic stroke and myocardial infarction).

In summary, whilst it is agreed that a reduction in primary endpoint events as numerically described in the APEX study could be of clinical relevance, efficacy has not been established, as the results cannot be considered robust and statistically compelling. In addition, as outlined under Ground #3, efficacy has to be assessed in the context of safety concerns primarily related to bleeding events.

Ground #3-Benefit-risk profile

The comparison across studies investigating different DOACs in different indications was not considered of importance by the CHMP especially considering that a variety of doses was used in a variety of patients with different baseline bleeding risks and co-medications.

The applicant indicated that a positive B/R balance has been demonstrated for the overall group including patients in the 80mg and the 40 mg stratum (renal failure, treatment with P-gp Inhibitors) based on demonstrated efficacy and the lack of an increase in major bleeding events with a numerically lower rate of intracranial bleeding events. The increase in CRNM bleeding events was considered to be readily manageable by the Applicant. After exclusion of patients in the 40 mg stratum due to a higher bleeding rate, the B/R in the 80 mg stratum was considered even more favourable.

Major Bleeding events

The CHMP noted that there was an imbalance in intracranial haemorrhages favouring betrixaxban and an imbalance in gastrointestinal bleedings favouring enoxaparin.

The incidence of intracranial haemorrhages (ICH) through 7 days after discontinuation of all study medication was lower in the betrixaban group (n = 2 [0.05%] vs. n = 7 [0.19%]). When including a fatal event, it was 2 vs. 8 events. As discussed during the initial evaluation no final conclusions can be drawn from this result due to the small number of events.

However, the numerical advantage in ICHs is contrasted by an increase in major gastrointestinal (GI) bleedings (betrixaban 19 vs. enoxaparin 9).

Clinically relevant non major (CRNM) bleeding events

CRNM were defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study treatment, or associated with discomfort for the patient such as pain or impairment of activities of daily life.

The incidences of Major and CRNM bleedings requiring hospitalization were slightly higher in the betrixaban group than in the enoxaparin group, 0.97 vs. 0.78%, respectively. According to the follow-up information in the overall safety population, the numbers of Major or CRNM bleeds that required medical/surgical consultation were 94 vs. 50 in the betrixaban and enoxaparin groups, respectively, medical/surgical intervention 41 vs. 22, hospitalization 23 vs. 14, study drug interruption 18 vs. 4 and study drug discontinuation 68 vs. 38, respectively. These differences are considered clinically relevant.

When comparing bleeding events and symptomatic primary efficacy events it is important to bear in mind that treatment with enoxaparin was continued for 10 ± 4 days only and that different treatment durations and two different drugs are compared. The time to event analysis suggests that efficacy was similar in both groups as long as patients were on treatment up to day 7 – 8 in both arms, whereas the rate of adjudicated major or CRNM bleeding events was immediately higher on Betrixaban from day 2 on. The observation raises the possibility that prolonged treatment with enoxaparin might have been associated with an overall lower rate of adjudicated major or CRNM bleeding events and efficacy comparable to that of betrixaban.

Clinically relevant non-major bleeding events may be a particular concern in elderly and fragile patients. It is unclear whether the bleeding pattern and severity would remain unchanged in clinical practice. As has been outlined in the initial evaluation, the long t1/2 may be a disadvantage in case of a bleeding event. The pronounced food effect may contribute to a higher variability in plasma levels and may affect efficacy and bleeding risk and thus B/R. This may be an issue for patients that lack appetite due to their illness and may take betrixaban without food.

Net clinical benefit

Several analyses have been provided during the procedure combining efficacy outcomes and bleeding events ("net clinical benefit). The results largely depend on whether CRNM bleeding events are included in the analysis or not. When including the most important events of symptomatic VTEs + Major bleeding events + all-cause mortality, RR was 0.91 – 0.98 for the three cohorts (80 + 40 mg) and 0.85 – 0.92 (80 mg only). When including CRNM bleeding events into the analysis, RR was 1.09 – 1.16 (80 + 40 mg) and 0.98 – 1.06 (80 mg only) for the three cohorts. For fatal or irreversible events

the RR was 0.69 – 0.74 but, as outlined above, events like myocardial infarction and stroke that were included in this analysis are normally not considered related to VTE events.

Benefit risk balance

The B/R balance of this product hinges mainly on three factors: the weight given to CRNM bleeding events, the robustness of the efficacy data, and whether an appropriate well-defined target population can be identified.

Compared to standard enoxaparin therapy CRNM bleeding events more than doubled in the combined 40 mg/80mg group but were still about 2-fold increased in the 80 mg stratum. In clinical practice outside of a clinical trial, the risk and clinical relevance may be higher especially in very elderly and/or fragile patients. Although it can be assumed that the more favourable data in the 80 mg group are more relevant with higher-risk patients from the 40 mg group being contraindicated, it is clear that the bleeding risk depends on intrinsic and extrinsic factors not all of which may be known. In addition, when assessing the head-to-head comparison during the first 7 – 8 days of treatment, CRNM bleeding risk appeared to be higher on betrixaban than on enoxaparin. This raises the question whether in an overlapping population like the one investigated in EXCLAIM bleeding risk would be considered inappropriately high. Overall, it is likely that the risk of clinically relevant bleedings is even higher and more difficult to control in clinical practice compared to a well-controlled clinical trial setting.

The issues of the robustness of the data and the concerns regarding the identification of an appropriate target population have been discussed in detail in the second ground for re-examination (and during the intial evaluation of this application). Since it was the primary hypothesis that patients at a very high risk as identified by D-dimer testing would be the ones with the best B/R balance, this is the hypothesis that has to be tested in accordance with the requirements for one pivotal trial. When considering the overall broader population as being the relevant one, confirmation by an additional study is required considering that previously three studies with a largely overlapping patient population have failed to show a positive B/R balance of extended treatment with anticoagulants.

Ground #4-Learnings from prior VTE prophylaxis trials and its precedent

The applicant argued that there are three relevant aspects which distinguish the APEX study from the three failed studies EXCLAIM, MAGELLAN and ADOPT: The choice of the dose, the pharmacokinetic profile of Betrixaban and the selection of a population enriched for high risk of VTE events.

The CHMP agreed that that dose selection and PK properties are important in the B/R evaluation of anti-coagulants. Nevertheless the CHMP stressed that it cannot be assumed *a priori* that a long t ½ is an advantage per se. E.g. for edoxaban which has a short t1/2, qd administration has been considered more appropriate to avoid bleeding events instead of bid despite of a higher peak trough ratio.

The key primary hypothesis of APEX was that patients at higher baseline risk as identified by D-dimer testing would show a better efficacy. This hypothesis was not confirmed. Absolute risk reduction was similar and relative risk reduction was numerically lower in these patients compared with the overall APEX population. This indicates that identifying an appropriate patient population is not just about identifying high risk, which may have been a reasonable assumption at the time the study was designed. As has been discussed, in some patients asymptomatic DVTs may be more an indicator of severe terminal disease that itself is not affected by anticoagulant therapy.

Moreover, there is large overlap between patients in APEX and in the other trials. E.g. In ADOPT more than 1/3 of the patients had heart failure NYHA class III or IV, 3 – 3.5% had active cancer, 37% acute respiratory failure. The primary event rate was 2.7 – 3.0 which is similar to the risk in those patients included in the overall APEX population that did not fulfil the D-dimer criterion.

Clearly identifying a target population is also important when transferring data from clinical studies to clinical practice. Patient populations included in clinical trials usually differ to some degree from patients treated thereafter in clinical practice. Bleeding risks may be more important outside the surveillance program of a clinical trial. With narrow therapeutic index anticoagulants, results have to be particularly robust to such differences and the population with an established positive B/R has to be clearly defined. This is in question in light of 3 failed studies in an overlapping population and a failed hypothesis in APEX that patients at highest risk might have the highest benefit.

Selection of patients with a positive B/R obviously remains a difficult task since both a relevant benefit and an acceptable bleeding risk has to be demonstrated based on robust data. In the light of 3 failed studies in overlapping patient populations it is questionable whether a subsequent single fourth study even without the statistical issues discussed above would have been acceptable as being sufficient to support a new treatment paradigm.

According to "Points to consider on application with 1. meta-analyses; 2. one pivotal study. (CPMP/EWP/2330/99)", a therapeutic area with a history of failed studies or failures to confirm seemingly convincing results would be an important reason not to pursue approval based on a single pivotal trial.

Ground #5-Biological plausibility in VTE prophylaxis

There is a biological and medical rationale for an extended treatment in medically ill patients at increased risk for the development of VTE events due to the remaining risk of VTE events after early cessation of anticoagulant treatment. However, a robust positive B/R relationship has to be established, which is not the case for betrixaban.

6. Benefit-risk balance following re-examination

6.1. Therapeutic Context

6.1.1. Disease or condition

See Section 3.1.1

6.1.2. Available therapies and unmet medical need

See Section 3.1.2

6.1.3. Main clinical studies

See Section 3.1.3

6.2. Favourable effects

The primary outcome was a composite endpoint comprising the occurrence of any of the following events asymptomatic proximal DVT (as detected by ultrasound) until Day 47, Symptomatic DVT (proximal or distal), Non-fatal PE, or VTE-related death through Visit 3 (i.e. up to Day 47).

The event rates (95% CI) % for step 1 in the primary analysis in Cohort 1 was 8.5 (7.3-9.7) % in the enoxaparin arm and 6.9 (5.8-8.0) % in the betrixaban arm (p=0.054). Thus, superiority vs standard of care with Enoxaparin was not formally demonstrated for Betrixaban.

The applicant conducted an alternative analysis of the primary efficacy endpoint based on the post-hoc PEOP including one additional patient (patient X) in the enoxaparin arm who had an event, which reduced the p-value in the analysis of Cohort 1 from 0.054 to 0.048. The applicant considered the post-hoc inclusion of this event, which was based on clinical evaluation in accordance with the intent of the SAP, as justified and considers that the resulting p-value supports formal evaluation of step 2 (Cohort 2) and step 3 (cohort 3, the entire study population).

In Cohort 2 and the overall population, the nominal p-values for the comparison between betrixaban and the comparator are lower than in Cohort 1 (and clearly below 0.05). The event rate (95% CI) % for the primary efficacy analysis in the overall primary efficacy population was 5.3 (4.5-6.1) % for Betrixaban and 7.0 (6.1-7.9) % for the comparator (nominal p-value=0.006). However it was noted that the ARR using the point estimate are similar in Cohort 1, Cohort 2 and the overall population.

The primary efficacy outcome in Cohort 1 was also analysed in pre-specified subgroups. In the analysis by dosing criteria, patients randomized to 80 mg betrixaban, i.e. excluding patients receiving 40mg due to severe renal insufficiency or need for a strong P-gp inhibitor had an event rate of 6.3% vs. 8.4% in patients receiving enoxaparin (nominal p = 0.026).

For patients with severe renal insufficiency, the event rate was 10.2% in the betrixaban group (11/108) vs 12.7% in the enoxaparin group (10/79) (nominal p=0.598). For patients on strong P-gp inhibitors, the event rate was 8.5% (29/342) in the betrixaban group vs 7.9% (28/356) in the enoxaparin group (nominal p=0.767).

The first secondary efficacy analysis included only symptomatic events. The event rates (95% CI) % for Cohort 1 in the analysis of the first secondary efficacy endpoint was 1.3 (0.8-1.8) % for betrixaban and 1.9 (1.4-2.5) % for the comparator (nominal p-value 0.092). The event rates (95% CI) % were 0.9 (0.6-1.3) % for betrixaban and 1.5 (1.1-1.8) % for the comparator in the overall population (nominal p-value= 0.039)

The second secondary endpoint was similar to the composite primary efficacy endpoint except that VTE-related death was changed to all-cause mortality. This is the endpoint that is proposed by the relevant CHMP guideline (EMA/CPMP/EWP/6235/04 Rev. 1) to be used as the primary efficacy endpoint in a confirmatory superiority trial. The event rate (95% CI) % for the second secondary efficacy outcome in Cohort 1 was 11.5 (10.1-12.9) % for betrixaban and 12.9 (11.4-14.3) % for the comparator (nominal p-value=0.164). The event rate (95% CI) % in the overall population was 9.2 (8.2-10.2) % for betrixaban and 10.9 (9.8-11.9) % for the comparator (nominal p-value=0.024).

6.3. Uncertainties and limitations about favourable effects

Several aspects of the design of the APEX study make it difficult to define the target population that would benefit from prolonged treatment with betrixaban with sufficient certainty: the critical place of D-dimer testing in the assessment of whether patients were eligible to the study, the many amendments of the inclusion and exclusion criteria that were implemented during the course of the study, questions pertaining to the immobilization status and severity of the acute medical illness of the included subjects. Moreover, the absence of patients with active cancer constitutes a lack of data in a population at high risk of both VTE and bleeding.

Betrixaban was not shown to be superior to enoxaparin, according to the pre-specified closed testing, gate-keeping procedure in Cohort 1. Even accepting the alternative analysis including patient X resulted in a borderline statistical significance, which raises significant concerns over the robustness of the reported results. The APEX study was a large study including thousands of patients where statistical significance should not be affected by the inclusion or exclusion of one patient in the analysis. This is even more important in the context of a new medicinal product with no established favourable Benefit/Risk in any indication and which is trying to establish a new treatment paradigm.

There is further uncertainty due to missing data mostly due to patients that did not have an evaluable ultrasound result between Day 32 and Day 47 (and no symptomatic event). This number was higher in the betrixaban group than in the comparator group. Considering that severe disease is associated with a higher risk for asymptomatic DVT but may also be the reason for not showing up for ultrasound testing, the overall high rate of ultrasound drop-outs and the difference in ultrasound drop-out rates between the groups could have influenced the outcome of the primary endpoint in favour of Betrixaban.

The applicant explored the issue of missing data by providing sensitivity analyses using multiple imputation to handle those with missing assessments under two different underlying assumptions. In the Missing At Random analysis (excluding patient X) the results for the primary endpoint were; for Cohort 1: ARR = 1.6% and p = 0.11 and in the overall population: ARR = 1.7% and p = 0.008, and thus quite similar to the outcome in the primary analysis of the primary endpoint. In the Jump To Reference analysis (excluding patient X) the results were for Cohort 1: ARR= 1.31 and p-value=0.219 and for the overall population: AR= 1.46 and p-value=0.027, i.e. smaller compared to the outcome in the primary analysis of the primary endpoint. In addition, a tipping point analysis was performed. From these analyses it is evident that the findings in Cohort 1 are not robust.

6.4. Unfavourable effects

One fatal bleeding occurred in each group (0.03%). Major bleeding events occurred with similar frequencies in the two treatment groups, (0.67% vs. 0.57% in the betrixaban and enoxaparin arms, respectively). A lower rate in intracranial (0.05% vs. 0.17%) and a higher rate of gastrointestinal (0.51% vs. 0.24%) major bleedings was observed in the betrixaban group. CRNM [clinically relevant non major] bleedings were more frequent in the overall betrixaban group (2.45% [95% CI 1.95; 2.95] vs. 1.02% [0.70; 1.35]). CRNM bleedings included haematuria, epistaxis, rectal and upper GI bleedings. Therefore, in the composite of Major or CRNM bleedings, there was a clear difference in the incidence of these events in favour of standard therapy with enoxaparin (3.12 vs 1.59%, nominal p-value <0.001).

Approximately 50% of the CRNM bleedings in both groups were classified as severe adverse events (n=46 vs. 18 in the betrixaban and enoxaparin groups, respectively).

Head to head comparison of betrixaban vs standard of care showed an increased risk of major or CRNM bleeding with betrixaban during the first 7 – 8 days of the APEX study, i.e. during the period when all patients where on anti-coagulant treatment.

The incidences of Major and CRNM bleedings requiring hospitalization were slightly higher in the betrixaban group than in the enoxaparin group, 0.97 vs. 0.78%, respectively. According to the follow-up information in the overall safety population, the numbers of Major or CRNM bleeds that required medical/surgical consultation were 94 vs. 50 in the betrixaban and enoxaparin groups, respectively, medical/surgical intervention 41 vs. 22, hospitalization 23 vs. 14, study drug interruption 18 vs. 4 and study drug discontinuation 68 vs. 38, respectively.

In the 80 mg dose group, the ARR of Major and CRNM bleedings for enoxaparin compared to betrixaban was lower (-1.07%), compared to the whole trial population (-1.53 %). The mortality rates were similar in the two treatment groups (6 %) and with similar distributions of adjudicated causes of death.

Differences between the two treatment groups of other adverse events were generally small and similar in the overall study population and in Cohorts 1 and 2.

6.5. Uncertainties and limitations about unfavourable effects

The higher incidence of clinically relevant bleedings among the betrixaban treated patients is of concern. The longer half-life of betrixaban compared to other oral anti-coagulants and the pronounced food effect might render the management of such events more problematic in this fragile and elderly target population.

In the 40 mg dose group, the incidences of major or CRNM bleedings were 4.79 vs 1.38% in the betrixaban and enoxaparin groups, respectively (ARR -3.42, 95% CI -5.18, -1.65). It was agreed with the Applicant that the 40 mg dose group probably represents a more vulnerable subgroup of patients. However, it is of some concern that, despite the relatively higher incidence of thrombotic events in this lower dose group, to some extent probably due to a generally lower exposure of betrixaban than in the overall study population, the difference in bleeding rates vs. enoxaparin seems to increase. It is therefore difficult to draw any conclusions regarding a correlation between betrixaban plasma levels and the risk of bleeding.

As only one dose level was studied in APEX, information is lacking regarding the therapeutic window (exposure-response relationship on hard endpoints) of betrixaban. Without such information, any changes in plasma concentrations are hard to evaluate.

The relative increase in clinically relevant non major bleedings observed with betrixaban is approximately similar to the increases seen in the ADOPT and MAGELLAN studies investigating use of other Xa inhibitors for extended thromboprophylaxis (approximately doubled) where the B/R balance was considered negative. Dissimilar to these studies, in APEX the overall rate of major bleedings was not increased whereas in ADOPT and MAGELLAN the RR was more than doubled. There are however remaining uncertainties on the relative anti-haemostatic potency of betrixaban as compared to other Xa inhibitors. This is partly due to the limited clinical experience with betrixaban in other populations than the one now aimed for. There is however no reason to expect that the distribution of bleedings of different severity would be different for betrixaban than for other Xa inhibitors. This is supported by the observation that, consistent with other Xa inhibitors, the rate of intracranial haemorrhages was lower whereas the risk of gastrointestinal major bleeding events was higher compared with enoxaparin. Thus, in the large target population proposed by the applicant bleedings typically associated with Xa inhibition (including ISTH major bleedings) would be expected to increase to a similar extent in relative terms and with a similar pattern.

6.6. Effects Table

Table 55. Effects Table for betrixaban in the prophylaxis of venous thromboembolism (VTE) in adults hospitalised for an acute medical illness (data cut-off:15 January 2016)

Effect	Short Description	Unit	Betrixaban	Enoxaparin	Uncertainties/ Strength of evidence	References
Favourable Effects						
Composite endpoint: 1) Asymptomatic proximal DVT 2)Symptomatic DVT 3) Non-fatal PE, or 4) VTE-related death	Occurrence of any of the events through Visit 3 (=35 days ± 7 days)	% (95 % CI)	6.90 (5.8-8.0)	8.49 (7.3-9.7)	p=0.054. Statistical significance achieved in an alternative analysis including an additional patient in the control arm, p=0.048. Superiority of betrixaban not demonstrated	APEX, Cohort 1 of the PEOP
Unfavourable Effects						
Major or CRNM bleedings	Events occurring through 7 days after treatment discontinuation	%	3.12	1.59	Nominal p-value <0.001	APEX

Abbreviations: CRNM: Clinically Relevant Non-Major bleedings, DVT: Deep Vein Thrombosis, PE: Pulmonary Embolism, PEOP: Primary Efficacy Outcome Population

Notes: Betrixaban was compared to enoxaparin through a closed testing, gate-keeping procedure that sequentially tested the primary and secondary efficacy composite outcome hypothesis in each of the 3

Cohorts in seven steps. Cohort 1 included patients who have D-dimer ≥2 x ULN at baseline and Cohort 2 included patients who have D-dimer ≥ 2 x ULN and/or age ≥75 years. As superiority not demonstrated in Cohort 1, subsequent analyses were considered exploratory.

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

VTE is an important complication in acute medically ill patients. The risk of VTE events is highest during the first period of the illness, which is usually characterised by immobilisation, but may persist for several weeks afterwards. With the advent of safe oral anti-coagulants, extending the usual period of VTE prophylaxis seems viable. However, multiple efforts to demonstrate a favourable B/R for an extended treatment regimen have failed, either because of lack of efficacy an/or excess in bleeding.

For betrixaban there is a numerical advantage compared to enoxaparin in the reduction of VTE events in the overall APEX population which is driven by a reduction in asymptomatic VTE. The importance of these events is not entirely clear. In a clinical trial setting, therapy would be initiated after a positive trial-mandated ultrasound thereby usually preventing further adverse outcomes. In practice, asymptomatic VTE events would not trigger hospitalisation and only if the event would become symptomatic at a later time-point, effective therapy would be started.

Importantly, the statistical test strategy set out by the applicant formally failed in showing superiority of Betrixaban over standard of care with Enoxaparin in the first Cohort tested (patients who have D-dimer ≥ 2 x ULN at baseline). Even though superiority appeared to be shown in the overall primary efficacy population, this analysis should formally be regarded as exploratory according to the test procedure put forth by the applicant.

The applicant conducted an alternative analysis of the primary efficacy endpoint based on the post-hoc PEOP including one additional patient (patient X) in the enoxaparin arm who had an event whereby the p-value in the analysis of Cohort 1 changed from 0.054 to 0.048. The applicant considered that post-hoc inclusion of this event, which was based on clinical evaluation in accordance with the intent of the SAP, is justified and yields a p-value supporting formal evaluation of Cohort 1 and the entire study population.

Formally, by including patient X, the study was successful. However, the results can still by no means be considered statistically compelling, especially in the context of a single pivotal trial.

The applicant provided a number of possible explanations for the failure of the study. These explanations include inadequate dosing, especially of individuals with renal insufficiency and the use of suboptimal D-dimer testing for classifying study subjects. Whilst some of these explanations appear reasonable, this does not change the fact that the study did not formally meet its predefined primary endpoint and, even if patient X would be included in the analysis, the results of the primary analysis can by no means be considered compelling. Therefore, superior efficacy vs established standard of care has not been established. A second trial (in which the experience and acquired knowledge, for example on correct dosing for patients with renal failure could be of use for the planning and design of the study) is required.

There are a number of additional uncertainties and limitations of the data which affect the importance of the favourable effects observed. These pertain to the difficulties to define the intended target population based on available data, the potential impact that the many protocol amendments may

have on the overall findings of the study, the interpretation/estimation of the primary efficacy outcome in light of the relevant amount of missing data on the primary efficacy endpoint and which are unevenly distributed among the treatment groups.

Regarding unfavourable effects, the most important risk in association with betrixaban use is the risk of bleeding.

Major bleeding events occurred with similar frequency in both groups, with a lower rate of intracranial bleedings and a higher rate of gastrointestinal bleedings in the betrixaban treated patients. CRNM bleedings were about two-fold increased in the betrixaban group. In clinical practice there is no clear distinction between the two categories of bleedings, especially as the ISTH criteria for classification are considered rather conservative. Therefore, the overall bleeding pattern is of greater importance.

CRNMB events are at least as problematic as symptomatic VTE, because many of these were associated with hospitalisation and other sequelae. CRNM bleedings included haematuria, epistaxis, rectal and upper GI bleedings. Approximately 50% of them were classified as SAE. The observed increased incidence of CRNM bleedings is of concern in the fragile, and often elderly, patients that can be expected to continue treatment for several weeks after discharge from hospital. Moreover, the comparatively slow elimination rate of betrixaban as well as the markedly increased exposure in fasting state may also have implications in minimising and managing these bleeding events in clinical practice.

In the time to event analysis, no difference in efficacy was observed between enoxaparin and betrixaban during the first 7 – 8 days when all patients were on active treatment, whereas bleeding rates were higher in the betrixaban arm during this time. This raises the question, whether non-inferiority of betrixaban vs. enoxaparin could have been shown for safety if prolonged treatment with enoxaparin would have been investigated in the trial. This is of particular concern since bleeding rates of extended treatment with enoxaparin appeared to be unfavourable in the EXCLAIM study.

6.7.2. Balance of benefits and risks

From the data presented by the applicant, it is concluded that the favourable effects of betrixaban in terms of VTE prophylaxis for the proposed indication and posology have not been robustly demonstrated and, do not outweigh the increased risk of clinically relevant bleeding events.

The target population with a positive B/R balance is not sufficiently defined and the increased risk of clinically relevant bleedings may translate into serious complications in the proposed target population, which most likely will have both comorbidities and co medications. In addition, some of these patients could have a poor food intake which would potentially increase their risk of bleedings since taking betrixaban under fasting conditions is expected to increase exposure of the drug.

In addition, the results with betrixaban also need to be seen in context with three previous trials that had failed to show a positive B/R of prolonged vs. short term anticoagulant treatment in an overlapping patient population. This also has an impact on the level of certainty of the results required before these can be considered compelling both in terms of the degree of statistical significance and its clinical relevance. These requirements have not been satisfied by the results from the APEX study.

6.7.3. Additional considerations on the benefit-risk balance

During the Oral Explanation at the CHMP, the applicant requested a conditional marketing authorisation approval for Dexxience, subject to a product registry which would be implemented in the post-authorisation phase.

The CHMP considered the new proposal and concluded that as a positive benefit/risk balance could not be established for Dexxience, a conditional marketing authorisation could not be granted.

6.8. Conclusions

The overall B/R of Dexxience is negative.

7. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion andthe applicant`s proposal for a conditional marketing authorisation in its final opinion concluded by consensus that the safety and efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the marketing authorisation for the above mentioned medicinal product.

Whereas

Reviewing the APEX study in the context of efficacy and safety data from oral factor Xa inhibitors in extended prophylaxis of venous thromboembolism, the CHMP considers that a favourable benefit/risk ratio of Dexxience in the proposed indication has not been robustly demonstrated.

- The efficacy of Dexxience in the proposed indication has not been robustly demonstrated. Evidence presented was based on a single pivotal study, without confirmation of efficacy for betrixaban in other indications. In the APEX study, the first step of the statistical testing (according to the pre-specified closed testing gate keeping procedure) of the primary endpoint did not robustly establish compelling evidence of efficacy.
- Treatment with Dexxience was associated with an increased risk of bleeding events (major or clinically relevant non major bleedings) compared to the comparator in the trial (both during the first 6-14 days in comparison to enoxaparin and at the end of the trial). This is a serious concern considering that the target population comprises patients with comorbidities for which potential bleedings may have serious consequences. This is further compounded by the pharmacokinetic properties of Dexxience, which could have significant implications for the occurrence and management of such events in clinical practice. The APEX study alone does not address all uncertainties on the risk of bleeding events associated with Dexxience.

Due to the aforementioned concerns, a satisfactory summary of product characteristics, labelling, package leaflet, and risk management plan cannot be agreed at this stage.