CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208383Orig1s000

CLINICAL/STATISTICAL REVIEW(S)

COMBINED CLINICAL & STATISTICAL REVIEW

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Application Number(s)	208383
Priority or Standard	Priority
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Division / Office	DHP/OHOP
Reviewer Name(s)	Saleh Ayache, MD Xin Gao, Ph.D.
Review Completion Date	03/23/2017
Established Name	Betrixaban
(Proposed) Trade Name	BevyxXa
Therapeutic Class	Factor Xa inhibitor
Applicant	Portola Pharmaceuticals, Inc.
Formulation(s)	Capsule for oral administration
Dosing Regimen	An initial single dose of 160 mg, followed by 80 mg once daily, taken at the same time each day with food.
Indication(s)	For extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE
Intended Population(s)	Hospitalized Patients for Acute Medical illness

Template Version: March 6, 2009

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Table of Abbreviations

AE	Adverse event
AF	Atrial Fibrillation
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APEX	Acute Medically Ill Prevention with Extended Duration Betrixaban Study
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
BID	Twice daily
BMI	Body Mass Index
CVA	Cerebrovascular accident
CEC	Clinical Events Committee
Cmax	Peak serum concentration
CHF	Congestive Heart Failure
CrCL	Creatinine clearance
CRNM	Clinically Relevant Non-Major
CUS	Compression Ultrasound Sonography
DD-	D-dimer negative (i.e., D-dimer < 2 x ULN)
DD+	D-dimer positive (i.e., D-dimer ≥ 2 x ULN)
DVT	Deep vein thrombosis
DHP	Divisions of Hematology Products
DCRP	Division of Cardiovascular and Renal products
eCTD	Electronic Common Technical Document
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EQOL	Economic and Quality of Life
FXa	Factor Xa
GCP	Good Clinical Practice
GI	Gastrointestinal
Hgb	Hemoglobin
ICH	Intracranial hemorrhage
INR	International normalized ratio
ISTH	International Society of Thrombosis and Hemostasis
IXRS	Interactive voice/web response system
LFT	Liver function test
LMWH	Low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-treat
MI	Myocardial infarction
PD	Pharmacodynamic
PEOP	Primary Efficacy Outcome Population
P-gp	Permeability Glycoprotein
PK	Pharmacokinetic
PO	Orally/by mouth

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PE	Pulmonary embolism
PPI	Proton Pump Inhibitor
QD	Once daily
RR	Relative risk
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System Organ Class
SQ	Subcutaneous(ly)
TEAE	Treatment Emergent Adverse Event
TG	Thrombin Generation
TIA	Transient Ischemic Attack
TKR	Total Knee Replacement
ULN	Upper Limit of normal
VTE	Venous Thromboembolism
WNL	Within normal limits

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical review team finds a favorable benefit-risk profile for betrixaban for prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE. Betrixaban should be approved for this indication.

1.2 Risk Benefit Assessment

The overall benefit of betrixaban prophylaxis is considered to outweigh the risk for prophylaxis of venous thromboembolism (deep vein thrombosis (DVT) and/or pulmonary embolism (PE)) in adult patients hospitalized for acute medical illness who had restricted mobility and other risk factors for venous thromboembolism (VTE).

Betrixaban is a Factor Xa (FXa) inhibitor that selectively blocks the active site of FXa. Approval is being sought for the use of betrixaban for extended duration (up to 42 days) prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with high risk factors for VTE. In support of the indication, the Applicant has submitted the data from one clinical trial 11-019 Study (APEX Study).

APEX was a randomized, double blind, multinational study comparing extended duration of betrixaban (for 35 to 42 days) to short duration of enoxaparin (for 6 to 14 days) in the prevention of venous thromboembolic events (VTE) in an acutely medically ill hospitalized population with risk factors for VTE. Eligible patients included adults 40 years of age or older, expected to be hospitalized for least 3 days for a specified acute medical illness (heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke), and had moderate or severe immobility for at least 24 hours and had an additional risk factor for VTE. In addition, eligible patients needed to have any one of the following additional risk factors for VTE:

- ≥ 75 years of age, or
- 60 through 74 years of age with D-dimer ≥ 2 ULN, or
- 40 through 59 years of age with D-dimer ≥ 2 ULN and a history of either VTE (DVT or PE) or cancer (excluding non-melanoma carcinoma of the skin)

The APEX trial excluded patients whose condition required prolonged anticoagulation (e.g., concurrent VTE, atrial fibrillation, cardiac valve prosthesis), were at increased risk of bleeding, had end stage disease with CrCL <15 mL/min or require dialysis, had severe renal insufficiency (CrCL 15-29 mL/min) and required the concomitant use of a P-gp inhibitor, had liver dysfunction, or were on dual anti-platelet therapy.

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Randomization was stratified by dosing and D-dimer status obtained from the local laboratory (D-dimer ≥ 2 x ULN vs. D-dimer < 2 x ULN). The dosing strata were defined:

- Betrixaban 80 mg [and enoxaparin placebo] or enoxaparin 40 mg [and betrixaban placebo] was given to patients who had neither severe renal insufficiency nor need for a concomitant strong P-gp inhibitor.

- Betrixaban 40 mg [and enoxaparin placebo] or enoxaparin 20 mg [and betrixaban placebo] for patients with severe renal insufficiency.

- Betrixaban 40 mg [and enoxaparin placebo] or enoxaparin 40 mg [and betrixaban placebo] for patients who were receiving a strong P-gp inhibitor without severe renal insufficiency.

Baseline characteristics were balanced between the treatment groups. The population was 55% female and 93% White, 2% Black, 0.2% Asian and 3.8% others. The most prevalent acute medical illness at hospitalization was acutely decompensated heart failure (45%), followed by acute infection without septic shock (29%), acute respiratory failure (12%), acute ischemic stroke (11%) and acute rheumatic disorders (3%). The mean age was 76.4 years and median age was 77 years, with 68% of patients ≥75 years of age, 97% were severely immobilized at study entry, and 62% had D-dimer ≥ 2 x ULN.

The primary efficacy endpoint was a composite of asymptomatic proximal deep-vein thrombosis (DVT) between day 32 and day 47, symptomatic proximal or distal deep-vein thrombosis, symptomatic nonfatal pulmonary embolism (PE), or death from venous thromboembolism occurred between day 1 and day 42. While the study was ongoing (after 35% enrollment) the protocol was amended to enrich the study with high risk patients by restricting further enrollment to patients with elevated D-dimer ≥ 2 x ULN or age of 75 years or older. The statistical analysis plan was modified to establish two cohorts.

- Cohort 1 included patients who had an elevated baseline D-dimer level (i.e., at least two times the upper limit of the normal range)
- Cohort 2 included the patients in Cohort 1 plus those who were 75 years of age or older.

In addition, a closed hypothesis testing procedure for the efficacy endpoints was established and the subgroup of patients in Cohort 1 was designated as the first primary efficacy analysis cohort. A second analysis population to be tested was Cohort 2, and a final analysis was defined as all evaluable patients (completed evaluation for every component of the primary endpoint) enrolled in the trial, formally if the initial hypothesis was tested statistically significant at 1-sided 0.025, and exploratory if not.

A total of 7,513 patients were randomized in 1:1 ratio to betrixaban group (n=3759) or enoxaparin group (n=3754). Patients were randomized to receive either:

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- Betrixaban: A loading dose of 160 mg betrixaban orally once daily for the first dose and then 80 mg once daily for 35 to 42 days and SQ enoxaparin placebo once daily for 6 to 14 days, or
- Enoxaparin: Enoxaparin dose of 40 mg SQ once daily for 6 to 14 days and oral betrixaban placebo once daily for 35 to 42 days.

Patients with severe renal insufficiency (creatinine clearance ≥ 15 and < 30 mL/min) received half of the dose of both study medications (betrixaban 80 mg loading dose, then 40 mg once daily or enoxaparin 20 mg once daily). Patients who took a strong concomitant P-gp inhibitor received a reduced dose of betrixaban (80 mg loading dose, then 40 mg once daily) or enoxaparin 40 mg once daily.

The primary efficacy outcome population (PEOP) defined as all patients randomized who received at least one dose of study drug and evaluated for every component of the primary endpoint was used for all efficacy analyses per statistical analysis plan (SAP). Based on this analysis population (PEOP), a total of 6286 patients (N=3112 for betrixaban and N=3174 for enoxaparin) were included in the PEOP.

The prespecified closed hypothesis testing procedure of the primary efficacy endpoint was first tested using Cohort 1 as defined by on the D-dimer levels determined by local laboratory for the combined 80 mg and 40 mg dose. The primary efficacy outcome in Cohort 1 of the PEOP occurred in 132/1914 (6.9%) patients of the betrixaban group and 166/1956 (8.5%) patients of the enoxaparin group, an absolute difference in event rate of 1.6%. The relative risk (RR) in the betrixaban arm relative to enoxaparin arm was 80.6% (95% CI [64.7%, 100.4%], P = 0.054). Since the pre-specified primary analysis for the primary endpoint in Cohort 1 failed to reach statistical significance based on the statistical plan, the interpretation of subsequent analyses will be regarded as exploratory.

Further exploratory analyses showed that the relative risk of the primary efficacy endpoint was 80% (95% CI [65.5%, 97.7%]) and 76% (95% CI [62.5%, 92.3%]) for Cohort 2 of the PEOP and overall PEOP, respectively.

Several key efficacy review issues are identified which may further complicate the interpretation of the results:

- The population of patients with D-dimer ≥ 2 x ULN or ≥ 75 years old is over sampled in the APEX study compared with general population in practice. Analysis results show heterogeneous efficacy in the enriched population vs. the non-enriched population (i.e. non-Cohort 1 appears to show better treatment effect). Interpretation of the efficacy results may need to take the sub-cohorts of the study population into consideration.

- The description of the study as using active comparator is misrepresentative. The treatment durations in the two treatment arms are not comparable (Betrixaban up to 35±7 days vs. Enoxaparin up to 10 ± 4 days). Also, patients received either SQ

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enoxaparin or enoxaparin placebo for short period of time (6- 14 days) while oral dosing was continued for the full treatment period duration.

- The occurrence of asymptomatic proximal DVT as detected by ultrasound was performed only on or before Day 47. Therefore, the APEX study did not provide sufficient data for adequate assessment of the time course of the treatment effect. The beneficial effect of "extended treatment' (i.e., after discontinuation of enoxaparin at day 6 to 14) cannot be separated from the treatment effect during the 6 to 14 days of enoxaparin active control period. Thus, the sponsor's proposed claim about extended effect can not be confirmed.

Based on exploratory analyses by dose level (40 mg, 80 mg), the 80 mg treatment group appears to show favorable results in reduction of VTE events. However, the assignment of dose levels was determined by baseline risk factor and/or concomitant medication (i.e. severe renal insufficiency; receive strong P-gp) and not by randomized assignment, thus the interpretation of the by-dose analysis results may be confounded by the patient population.

Even though the pre-specified analysis does not meet the pre-specified testing criteria based on Cohort 1 of PEOP, the beneficial effect of betrixaban for Cohort 1 appears to be supported by the results based on analyses using the modified Intent-to-Treat (mITT) population, D-dimer assessment per central laboratory measurement as well as different assessment window for the ultrasound evaluation.

The beneficial effect of betrixaban appears to also be supported by the results from Cohort 2, PEOP and mITT population when more patients are included. Furthermore, the subgroup analysis results based on the primary efficacy endpoint for Cohort 1 appear to be consistent. Based on these assessments, this reviewer confirms that betrixaban demonstrate favorable treatment effect based on the reduction of VTE events during 35±7 day treatment period, however, dose effect cannot be fully evaluated due to potential confounding and the actual effect of comparing betrixaban vs. enoxaparin cannot be determined from APEX due to non-comparable treatment duration, so additional results (following the analyses of Cohort 1) are presented descriptively.

Although, there were no statistically significant differences for the prespecified primary efficacy endpoint in Cohort 1 for the PEOP between the betrixaban group and the enoxaparin group in APEX trial, the clinical benefit of betrixaban prophylaxis appears to be supported by the results of prespecified sensitivity analyses of the primary efficacy endpoint from Cohort 2 for the PEOP, overall population for the PEOP and mITT when more patients with high risk for VTE were included. The results from prespecified exploratory sensitivity analyses showed consistent and robust clinical benefit of RR for VTE of 80%, 76% and 74.6%, respectively, for the extended duration betrixaban compared to shorter duration enoxaparin.

The major risk of betrixaban is bleeding. The rate of the primary safety endpoint of major bleeding event was reported for 25/3,716 (0.67%) patients in the betrixaban group and 21/3,716 (0.57%) patients in the enoxaparin group. Fatal bleeding was similar between the two groups with one fatal case reported in each group. There was a numerical increase in major

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gastrointestinal bleeds observed in the betrixaban group (20 cases) compared to the enoxaparin group (10 cases). However, there was a numerical decrease of major intracranial bleed in the betrixaban group (2 cases) compared the enoxaparin group (7 cases). The rate of major bleeding in the betrixaban group was 0.5% in patients who received 80 mg dose and 1.4% in patients who received a reduced dose of 40 mg.

The rate of major or clinically relevant non-major (CRNM) bleeds was higher in the betrixaban group than in the enoxaparin group (3.1% of patients vs. 1.6% of patients, respectively). The majority of CRNM bleeds that occurred in the betrixaban group (80%) were mild to moderate in severity and 60% of CRNM bleeding events did not required medical intervention. The median duration of CRNM bleeding was longer in the betrixaban group (3 days) compared to the enoxaparin group (2 days).

Based on the APEX study, the overall benefit of betrixaban treatment is considered to outweigh the risk for the proposed indication for prophylaxis of VTE (DVT and PE) in adult patients hospitalized for acute medical illness who had restricted mobility and other risk factors for venous thromboembolism (VTE).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

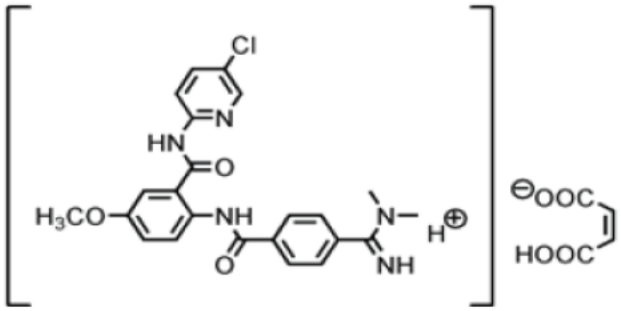
2.1 Product Information

Betrixaban is a benzamidine-based small molecule that blocks the active site of FXa. Activation of factor X to FXa via the intrinsic and extrinsic pathways plays a central role in the cascade of blood coagulation. By directly inhibiting FXa, betrixaban decreases thrombin generation.

Betrixaban capsules are immediate release, hard gelatin capsule formulations for oral administration. Betrixaban capsules are available for oral administration in strengths of 80 mg and 40 mg of betrixaban with the following inactive ingredients: dextrose monohydrate, croscarmellose sodium, magnesium stearate. The 40 mg capsules provided as gray (b) (4) /light blue (b) (4) size 4 hard gelatin capsules with “40” printed in black, rectified axially on the body and “PTLA” printed in white, rectified axially on the cap. The 80 mg capsules provided as gray (b) (4) /blue (b) (4) 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.

Proposed proprietary name: BevyxXa™
IUPAC Name: N-(5-chloropyridin-2-yl)-2-[4-(N,N-dimethylcarbamimidoyl)-benzoylamino]-5-methoxybenzamide maleate
Chemical Names: Carbamimidine Maleate (b) (4)
Molecular Formula: $C_{27}H_{26}ClN_5O_7$
Molecular Mass: 451.91 (free base)
567.98 (maleate salt)
Structural Formula: The structural formula of betrixaban is shown below.

Figure 1: Betrixaban structure



567.98

Source: NDA submission, module 2.3.S.1, P.2.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently there is no approved therapy for the proposed indication.

2.3 Availability of Proposed Active Ingredient in the United States

No product containing the active ingredient is approved in the U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

The main safety issue with anticoagulant products is bleeding. In addition, hepatotoxicity is safety concern that has been associated with oral anticoagulants.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

(b) (4)
IND 072679 for betrixaban was opened on October 10, 2005 (b) (4)

(b) (4)

The applicant met with the Agency on October 25, 2011 in an end of phase 2 (EOP2) meeting to discuss the phase 3 development for the (b) (4) indication for extended prophylaxis of VTE in acute medically ill patients. The Applicant submitted the initial protocol for the phase 3 (Study 11-019 APEX) on February 22, 2012 and recommendations were provided to the sponsor. A Type C meeting was held on January 21, 2014 to discuss potential enrichment strategy for the phase 3 trial. On Oct 2, 2015 a Fast Track designation was granted. The initial pediatric plan was agreed upon on September 20, 2016. The NDA was submitted on October 24, 2016 with a request for priority review. Priority review was granted based on that betrixaban is intended to prevent a serious life threatening disease where currently no approved drug is available. The PDUFA goal date is June 24, 2017.

2.6 Other Relevant Background Information

Venous thromboembolism (VTE) is associated with substantial long-term morbidity and reduced survival [(1)]. The American College of Chest Physicians guidelines recommended the use of low molecular-weight heparin [LMWH] for 6 to 14 days in acutely ill hospitalized medical patients to reduce the risk of thrombosis [(2)]. Randomized trials and observational studies have shown that the risk of VTE, including VTE related death following hospitalization continues in high risk acutely ill medical patients after discontinuation of standard of care in-hospital short duration VTE prophylaxis (recommended for 10 ± 4 days) with parenteral anticoagulants such as enoxaparin [(3,4,5)]. The Applicant's rationale to conduct the APEX trial was to demonstrate the benefit of extended duration VTE prophylaxis in decreasing the incidence of symptomatic and asymptomatic VTE events in hospitalized patients with acute medical illness.

In 2006 the Applicant conducted an open label, phase II/A, exploratory, multicenter, randomized, active comparator, parallel group study involving approximately 200 subjects undergoing unilateral total knee replacement. Patients were randomized in a 2:2:1 ratio to receive betrixaban 15 mg, betrixaban 40 mg, or enoxaparin 30 mg administered for 10 to 14 days. The primary efficacy endpoint was the incidence of VTE through the Day 10 to 14 visit following TKR where VTE was defined as proximal and/or distal DVT or PE. The primary efficacy endpoint (majority of VTEs included in the primary efficacy analysis were asymptomatic identified on the mandatory venogram) occurred in 14/70 (20%) patients in the betrixaban 15 mg dose group, 10/65 (15%) patients in the betrixaban 40 mg dose group and 4/40 (10%) patients in the enoxaparin 30 mg dose group. The applicant concluded that due to the small sample size used in this pilot study, no conclusions could be drawn regarding the relative efficacy of the 15 mg versus 40 mg dose of PRT054021 or of PRT054021 versus enoxaparin.

The Applicant also has conducted exploratory trials of betrixaban in patients with non-valvular atrial fibrillation (EXPLORE, PN-006). PN-006 was an open label, phase II trial to evaluate the pharmacokinetics and safety and tolerability of betrixaban in 189 adult patients with non-

valvular atrial fibrillation or atrial flutter. The main objective of this trial was to assess whether weight-based dosing provides equivalent C12 hr exposures between two weight groups (lower weight: < 80 kg, higher weight: ≥ 80 kg) and reduces betrixaban pharmacokinetic (PK) variability. The EXPLORE Study evaluated betrixaban for stroke prevention in 508 patients with atrial fibrillation comparing 3 months treatment with betrixaban 40 mg, 60 mg daily, and 80 mg daily to dose adjusted warfarin. One patient in each treatment arm had an event of stroke, MI, other systemic embolism or death. Major or clinically relevant non-major (CRNM) bleeding was reported in 1, 5, 5, and 7 patients in the treatment groups, respectively.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA submission contains the required components of the electronic Common Technical Document (eCTD). The overall quality and integrity of the application appear reasonable.

The initial filing review of the submission found the application fillable. But the following clinical concerns were noted:

- The proposed indication "for extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE" is very broad and does not appear to reflect the population that was studied in the submitted single pivotal trial (the APEX Study). The main inclusion criteria in the pivotal trial were age ≥ 40 years (≥90% of patients were age ≥ 65 years), anticipated to be severely immobilized for at least 24 hours after randomization and anticipated to be severely or moderately immobilized for ≥ 4 days after randomization and expected to be hospitalized for ≥ 3 days after randomization. However, the Applicant proposed indication is not restricted to hospitalized patients or severely to moderately immobilized patients or elderly. Wording of the indication will be a review issue.
- The Applicant claims that, although there were no significant differences between the prespecified primary efficacy between the two arms of the trial, the prespecified exploratory analyses provide evidence suggesting a clinical benefit from extended prophylactic treatment with betrixaban in prevention of venous thromboembolism (VTE).
- Adequacy of the support for efficacy from single pivotal trial will be a review issue.

3.2 Compliance with Good Clinical Practices

According to the study procedure a patient signed and dated informed consent form (ICF) written in a language in which the patient was fluent must be obtained prior to treatment for all enrolled. All participating centers were required to permit the independent ethics committees/institutional

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review boards a direct access to review the patient's original medical records for verification of study-related procedures and data.

The following sites were selected for an auditing review to be conducted by the Office of Compliance.

Table 1: Sites Inspected

Site # (Name, Address, Phone number, email, fax #)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
Dainis Krievins, MD Pauls Stradins Clinical University Hospital, Pilsonu Street 13, Riga, LV-1002, Latvia Ph: +37129450000 Fax: +37167069604 Email: (b) (6)	APEX study (Study 11-019)	229	for extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE.
De Pellegrin, Annamaria Presidio Ospedaliero di Vittorio Veneto Via Forlanini, 71 31029 Vittorio Veneto (TV) – Italy Phone: +390438665510 Fax: +390438665757 Email: annamaria.depellegrin@ulss7.it	APEX study (Study 11-019)	103	for extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE.
Valavicius, Arvydas Klaipeda University Hospital Department of Internal diseases Liepojos str. 41 LT-92288 Klaipeda Lithuania Phone: +370(6) 982 891 x2 Fax: +370(4) 639 669 x5 Email: (b) (6)	APEX study (Study 11-019)	65	for extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE.
Jim Welker, MD Anne Arundel Health System, 2001 Medical Parkway, Suite 203, Annapolis, MD 21401 Ph: (443) 481-1407 Fax: (443) 481-5896 Email: jwelker@aahs.org	APEX study (Study 11-019)	44	for extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE.

3.3 Financial Disclosures

In accordance with 21 CFR 54.4, the applicant submitted the required financial disclosure requirements and certification for the pivotal Phase 3 trial, Study 11-19. Portola stated that all principal investigators and most of the sub-investigators in Study 11-19, provided the required financial certifications which showed no financial arrangements that required disclosure.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Betrixaban maleate is manufactured in (b) (4)

(b) (4)

Reviewer comments: For further details refer to CMC review.

4.2 Clinical Microbiology

N/A

4.3 Preclinical Pharmacology/Toxicology

The antithrombotic and antihemostatic effects of betrixaban were evaluated in mice, rats, rabbits, monkeys, and baboons. In these studies, in vivo evaluation of betrixaban inhibition of venous thrombosis showed that betrixaban treatment resulted in dose-dependent reduction of clot formation and clot expansion. The evaluation of the effect of betrixaban on arterial thrombosis in animal studies revealed dose-dependent inhibition of arterial occlusion and a reduction in the time to arterial occlusion.

Bleeding effects from betrixaban administration were evaluated in mice (tail transection blood loss, rabbits (cuticle bleeding time), and monkeys (template bleed time). Betrixaban caused minimal to modest prolongation of bleeding times with increased blood loss at doses that were effective in the animal thrombosis models.

The toxicological effects of betrixaban was evaluated in rats and dogs and found to be safe at concentrations that were at least 9- to16-fold above the human therapeutic dose. Betrixaban was

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excreted in the bile of cannulated rats and caused biliary epithelial injury at high exposure in both rat and dog. The NOAEL for rats in the 6-month daily repeat oral gavage study was 150 mg/kg/day, and was associated with plasma drug exposures 94- to 102-fold greater than the anticipated human C_{max} or $AUC_{(0-24)}$ observed with the maximum proposed therapeutic dose of 80 mg/day.

In 6-month study in rats there were no adverse effects noted up to the highest dose (150 mg/kg/day) administered. The pharmacologic effect of prolonged PTs occurred at 200, 400, or 600 mg/kg/day when dosed for 14 or 90 days.

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. None of these studies indicated that betrixaban may be genotoxic or clastogenic.

Reviewer comments: For further details refer to nonclinical review.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Betrixaban is an oral FXa inhibitor that blocks the active site of factor Xa. Betrixaban does not require a cofactor (such as Anti-thrombin III) for activity. Activation of factor X to FXa via the intrinsic and extrinsic pathways plays a central role in the cascade of blood coagulation. By directly inhibiting FXa, betrixaban decreases thrombin generation (TG).

4.4.2 Pharmacodynamics

Betrixaban was evaluated in *in vitro* assays of tissue factor-initiated thrombin generation (TG) in human plasma and whole blood. Betrixaban produced dose-dependent inhibition of TG.

In vivo studies, betrixaban 15 and 40 mg BID doses were evaluated in patients undergoing unilateral knee replacement (EXPERT study). The mean observed plasma concentrations at steady state were 6.6 and 21.3 ng/mL for the 15 and 40 mg BID doses, respectively. The thrombin generation at betrixaban dose of 15 mg BID was similar to enoxaparin. However, the 40 mg BID betrixaban dose had a higher level of thrombin generation inhibition.

In the dose-finding study EXPLORE Xa in patients with documented non-valvular atrial fibrillation (AF), once daily doses of 40, 60, and 80 mg were evaluated. Three PD endpoints: anti-fXa activity, D-dimer, and TG were all assessed. The combined analysis allowed the dose selection of 80 mg for most patients in APEX, with dose reduction to 40 mg for patients on

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concomitant strong P-gp inhibitors and for those patients with severe renal impairment (CrCl > 15 mL/min and < 30 mL/min).

4.4.3 Pharmacokinetics

Betrixaban is orally absorbed rapidly and has a large volume of distribution that results in prolonged exposure. The predominant pathway of betrixaban metabolism is a non-CYP mediated (NADPH independent) amidolysis. This hydrolysis resulted in the formation of the polar compound, PRT062802 (N,N-dimethyl-4-carboxybenzamidine), which was the only prominent circulating metabolite observed in human plasma and the only prominent metabolite in human urine and feces in the mass balance study. Betrixaban has a larger biliary than renal elimination pathway. The effective half-life of betrixaban is approximately 19 to 27 hours.

Three phase 1 studies confirmed that betrixaban exposure (AUC) increased 2 to 3-fold by co-administration with the strong P-gp inhibitors, verapamil and ketoconazole. However, betrixaban found to be not a P-gp inhibitor after confirming that neither betrixaban nor digoxin affected the PK of the other compound.

Reviewer comments: For further details refer to Clinical Pharmacology review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

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Table 2: Clinical Trials

Trial ID/ Trial Type	Objectives	Study Design	Dose/Route of administration	Subjects	Duration
05-002 Food effect Phase 1	• Evaluate the single dose PK of a solid formulation betrixaban after a high-fat meal versus after an overnight fast • Provide pilot data on PK/PD in women vs men	Open label, 2-way crossover of 2 single doses, one dose after a 10-hour fast, and one dose after a high fat meal	Betrixaban dose 40 mg Oral Single dose	N=14 Healthy men or women between the ages of 18 and 60 years old, with a body mass index 19 to 28 kg/m^2	Two doses of 40 mg of betrixaban
04-001 Part 1 PK/PD; Phase 1	• Single dose PK of solid formulation 200 mg compared to the liquid formulation of the acetate salt • Evaluate the single dose PK of a solid formulation 200 mg administered 2 hrs after a light meal vs. after an overnight fast	Open label, 3-way crossover. Betrixaban 200 mg single doses of: solution (fasting), capsule (fasting), capsule (fed)	Betrixaban Dose 200 mg Oral	N= 9 Healthy males aged of 18 to 50 years. Part 1: 9 subjects	Single dose, on three occasions
04-001 Part 2 Dose Ranging	- Evaluate safety and tolerability of multiple oral doses of betrixaban over 10 days in healthy subjects - Define the PK and PD - Evaluate the effects of betrixaban on the QT interval	Double-blind, randomized, placebo controlled	Betrixaban 40, 80 or 120 mg BID, placebo, moxifloxacin	N=36 Healthy males aged of 18 to 50 years. Part 2: 36 subjects	PRT054021/PRT054021 Placebo: BID for 9 days and a single dose in Day 10. Moxifloxacin placebo: Days 1 to 10, Moxifloxacin: on Days 8 to 10.
02-401 Dose Ranging	•Assess the safety and tolerability of single ascending oral doses of betrixaban in healthy subjects and determine the maximum tolerated dose. •Establish the PK/PD of Single ascending doses of betrixaban in healthy subjects.	Double blind, randomized, placebo controlled, single ascending doses of betrixaban	Betrixaban doses 5 mg, 10 mg, 20 mg, 40 mg, 80 mg, 160 mg, 240 mg, 360 mg, 450 mg, 550 mg oral single dose	N=80 Healthy male subjects	Single ascending doses for maximum of 10 doses
07-009 DDI/ ketoconazole	Determine whether the co-administration of Ketoconazole affects the PK profile of betrixaban	Open label, Randomized sequence, 2-way crossover of 2 single doses of 40 mg betrixaban	Betrixaban Dose 40 mg Oral single dose	N= 12 Healthy subjects	4 weeks pre-dose, 1 week in the study unit on 2 occasions separated by a 12- to 14-day washout period
07-013	Examine the effects of	Double blind,	Betrixaban doses	N=96	The expected

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Thorurgh QT	betrixaban on the QTc interval	randomized, double - dummy, 4 period crossover	80 mg 140 mg Oral single dose	Healthy volunteers	study duration to complete all 4 treatment periods was up to 65 days.
05-003 (EXPERT) Efficacy/ Safety/PD Phase 2	-Exploratory efficacy data on betrixaban at doses of 15 and 40 mg PO BID compared to enoxaparin for the prevention of VTEs after unilateral TKR. -Provide pilot data on the safety of betrixaban at doses of 15 and 40 mg PO BID in the above subjects. -Assess the PK and PD of PRT054021 at doses of 15 and 40 mg PO BID	Phase II/A randomized, active control, parallel group study in patients undergoing total knee replacement (TKR). The study was open-label for randomization to enoxaparin vs PRT054021 maleate capsules, but the 15 mg vs 40 mg dose of PRT054021 was double-blind	15 mg betrixaban BID for 10-14 days 40 mg betrixaban BID for 10-14 days 30 mg enoxaparin SC twice daily for 10-14 days	N=215 Subjects were scheduled to undergo elective primary unilateral TKR	The duration of treatment for each patient was at least 3 months and no longer than approximately 11 months.
PN006 (DEC) Efficacy/ Safety/PD Phase 2	•Assess if weight-based dosing provides equivalent C12 hr exposures between 2 weight groups (< 80 kg, or ≥ 80 kg) and reduces PK variability. • Assess if targeted C12 hr exposure can be obtained with new formulation with food and with predefined adjustments •Safety and tolerability on long-term follow up.	Open label, Phase 2, parallel group, Dose exposure confirmation study	Betrixaban doses 30 mg 60 mg 90 mg Oral daily dosing for 25 days	N= 189 Study sample was to include at least 150 patients with a history of NVAF or atrial flutter (ECG or Holter documentation within past 12 months)	The total treatment with betrixaban was 24 weeks, which included the PK Phase (4 weeks) and the optional Safety Extension (20 weeks).
08-015 EXPLORE Efficacy and safety Phase 2	•Assess the safety and tolerability of betrixaban 40, 60, and 80 mg orally once daily for at least 3 months compared to dose-adjusted warfarin orally in patients with non-valvular atrial fibrillation (AF). •Provide preliminary efficacy data on betrixaban compared to dose-adjusted warfarin	Randomized, parallel group, dose-finding study of patients with documented nonvalvular atrial fibrillation (AF). Patients were randomized to oral warfarin or betrixaban 40, 60, or 80 mg once daily (1:1:1:1) for at	40 mg betrixaban QD for at least 12 weeks 60 mg betrixaban QD for at least 12 weeks 80 mg betrixaban QD for at least 12 weeks Warfarin dose adjusted to 2-3 INR	N=508 Patients with AF with indication for anticoagulation with a vitamin K antagonist and had at least one of risk factor for stroke such as age ≥75 years, prior stroke, symptomatic	Planned duration of treatment for each patient was at least 3 months and no longer than approximately 11 months

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	•Assess PK/PD of betrixaban at the above doses.	least 3 months of treatment.		CHF, or hypertension required treatment	
11-019 (APEX) Efficacy/ Safety Phase 3	- To demonstrate, in defined study cohorts, the superiority of extended duration (35-42 days) of betrixaban 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	Betrixaban doses 80 or 40 mg, based on renal function and P-gp inhibitor. Orally daily dosing for 35 days. Enoxaparin doses 40 or 20 mg, based on renal function and P-gp inhibitor. SQ daily for (10 ± 4 days)	N= 7513 Subjects who have been admitted to the hospital for acute heart failure, acute respiratory failure, acute infection, acute rheumatic disease and acute ischemic stroke. Subjects are severely or moderately immobilized and other risk factors for VTE.	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

Source: Modified from NDA submission, module 5.2, P. 1-22.

5.2 Review Strategy

This review is focused on safety and efficacy evidence that the applicant provided to support the proposed indication. Therefore, this review is driven by the proposed indication, including:

- Review focused on the single phase 3 randomized controlled trial APEX (Study 11-19) for efficacy.
- Safety data from pivotal trial APEX (Study 11-19).
- Examination of the study population eligibility to enter the trials.
- Review the Applicant's justification to conduct one trial to support new indication.
- Survey of current literature on the use of anticoagulant for VTE prophylaxis in acutely medically ill patients, using standard textbooks, reviews, references submitted by the Applicant and publications listed in PubMed.

5.3 Discussion of Individual Studies/Clinical Trials

APEX Study (Study 11-019)

Title: Multicenter, 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

Reference ID: 4076151

Primary Objective: Demonstrate 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.

Trial Design:
This was a randomized, double-blind, double-dummy, multicenter, multinational, superiority trial of 35 days (+ 7 day window, i.e., 35 to 42 days allowed) of oral betrixaban compared to short-term (10 ± 4 days) treatment with parenteral enoxaparin for the prevention of venous thromboembolic (VTE) events in patients who are at risk due to acute medical illness.

Eligible patients at high risk for VTE were randomized in ratio of 1:1 to receive either:

- Active betrixaban (either 80 or 40 mg PO QD) for 35 days (+ 7 day window) with enoxaparin placebo SQ QD for 10 ± 4 days (n=3759),

  OR
- Active enoxaparin (either 40 or 20 mg SQ QD) for 10 ± 4 days with betrixaban placebo for 35 days (+ 7 day window) (n=3754).

Each patient scheduled to have a follow-up visit 30 days (+ 5 day window) after Visit 3 (Day 35-42). Patients are allowed to take betrixaban or matching placebo for up to 7 days after Day 35 to accommodate Visit 3 scheduling. Each patient will receive follow-up after study drug discontinuation.

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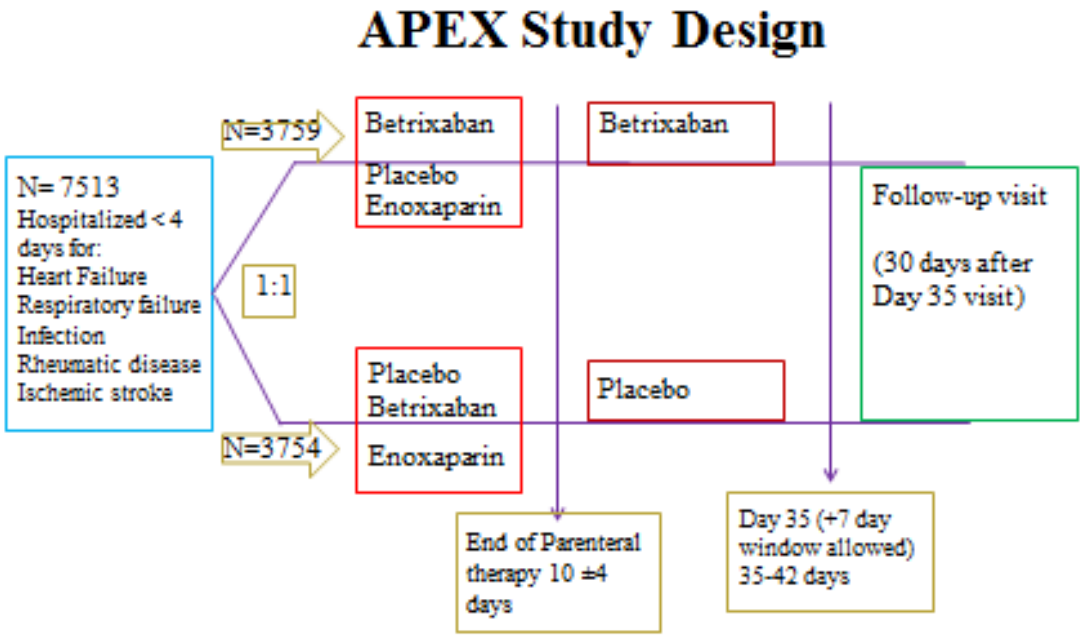
Figure 2: Study Design



Patients received an initial loading dose of 160 mg of oral betrixaban or betrixaban placebo followed by a single dose of 80 mg daily for 35-42 days, or enoxaparin or enoxaparin placebo 40 mg subcutaneous (SQ) injections for 10 ± 4 days.

Patients with severe renal insufficiency (CrCl ≥ 15 to < 30 mL/min) received half of the initial loading (80 mg) and daily dose (40 mg) of betrixaban or betrixaban placebo and half of the daily dose (20 mg) of enoxaparin or enoxaparin placebo.

Patients on a concomitant P-gp inhibitor received an initial loading dose of 80 mg of betrixaban or betrixaban placebo, then a reduced dose of 40 mg PO QD betrixaban and enoxaparin placebo SQ or 40 mg SQ QD enoxaparin and betrixaban placebo.

Reviewer comments: The trial design as stated by the Applicant "APEX was designed as an active-controlled superiority study to evaluate extended duration (35 to 42 days) anticoagulation with PO QD betrixaban for prevention of VTE in patients…" is misleading. In active control trial for a fair comparison, the duration of treatment in both treatment arms should be the same. However, in this trial the majority of the test drug (betrixaban) treatment period was compared placebo.

Eligibility Criteria:

Inclusion Criteria:

1. Male or female patients age ≥ 40 years. (Patients aged 40 to ≤ 60 years may be included only if they have as one of their additional Risk Factors for VTE, either previous history

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of VTE or history of cancer as listed under criterion # 6 below and meet the rest of the eligibility criteria).

2. Women of childbearing potential must have a negative serum pregnancy test prior to randomization and must be willing to use an acceptable method of contraception to avoid pregnancy throughout the study. Acceptable methods of contraception include tubal ligation, oral contraceptive, barrier methods (intra-uterine device, diaphragm, female condom, male condom). Abstinence is an acceptable form of contraception, only insofar as patients agree to use another acceptable method of birth control, preferably a barrier method, if they become sexually active.

3. Willing to sign informed consent and follow study procedures.

4. Patients must be anticipated to be severely immobilized for at least 24 hours after randomization and anticipated to be severely or moderately immobilized for ≥ 4 days after randomization in any type of care setting (e.g. hospital, intermediate care or rehabilitation center, managed care in home etc.) and with additional anticipated moderate mobility thereafter.

   Severe immobilization – Patient is totally confined by illness to bed or chair for 100% of time and is expected to have a very limited walking ability (distance of <10 meters). The patient may be able to use bedside commode with assistance.

   Moderate immobilization – Patient is confined by illness to bed or chair for more than 50% of the time during daytime hours. Patient cannot walk distance of 10 meters in 1 attempt or only able with difficulty. Mobility restricted to use of bathroom within a room.

5. Expected hospitalization of ≥ 3 days after randomization.

6. Patients must have one of the following as cause for the acute hospitalization:
   a. Acutely decompensated heart failure with chronic functional NYHA class II or greater and functional class III or IV on admission
   b. Acute respiratory failure in patients with chronic lung disease (please note patients with asthma not associated with chronic lung disease and patients with known bronchiectasis are excluded)
   c. Acute infection without septic shock
   d. Acute rheumatic disorders (including acute lumbar pain, sciatica, vertebral compression, rheumatoid arthritis, systemic lupus erythematosis, etc.)
   e. Acute ischemic stroke with lower extremity hemiparesis or hemi paralysis

7. Patient must have either:
   a. A D-dimer level (by local laboratory using the STAGO – LIA test or an ELISA method) of ≥ 2 x ULN within 4 days before randomization

   OR:

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b. At least two additional, documented Risk Factors as outlined below with the following constraints to the Primary Risk Factors:
   i. Age ≥ 75 years
   ii. Previous history of VTE (DVT or PE) or superficial venous thrombosis
   iii. Obesity (BMI > 35)
   iv. Previous documented chronic venous insufficiency or severe varicosis of the lower extremity
   v. Lower extremity paresis or hemiparesis or hemi paralysis Constraint: For patients with Primary Risk Criteria "e" the additional Risk Factor cannot include lower extremity paresis, hemiparesis or hemi paralysis
   vi. Hormone therapy (antiandrogen, estrogen, progesterone or selective estrogen receptor modulators (SERMs)).
   vii. History of cancer excluding non-melanoma carcinoma of the skin
   viii. Chronic heart failure (NYHA Class III or IV) Constraint: For patients with Primary Risk Criteria "a" the additional Risk Factor cannot include chronic heart failure
   ix. Chronic respiratory failure
   Constraint: For patients with Primary Risk Criteria "b" the additional Risk Factor cannot include chronic lung disease
   x. Active collagen vascular disease associated with limited mobility (e.g., isolated Sicca syndrome will not qualify)
   Constraint: For patients with Primary Risk Criteria "d" the additional Risk Factor cannot include active collagen vascular disease
   xi. Acute infectious disease contributing to current hospitalization
   Constraint: For patients with Primary Risk Criteria "c" the additional Risk Factor cannot include acute infectious disease contributing to current hospitalization
   xii. Current concomitant use of erythropoiesis stimulating agents
   xiii. Inherited or acquired thrombophilia

Exclusion Criteria:

1. Hospitalized > 96 hours before randomization (Timing of hospitalization begins when admitting orders are written)
2. Unable to take food by mouth (or by nasogastric/feeding tube, if one is in place)
3. Condition requiring prolonged anticoagulation (e.g., concurrent episode of VTE, atrial fibrillation, cardiac valve prosthesis, etc.)
4. Life expectancy < 8 weeks
5. In the opinion of the investigator it will not be possible to obtain an adequate bilateral compression ultrasound evaluation (e.g., patients with above the knee amputations)
6. Subjects unwilling or unable to comply with study procedures (including two ultrasound procedures) or medication instructions including the use of enoxaparin or matching placebo

At risk of increased bleeding due to:

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7. History of clinically significant bleeding (i.e., requiring medical attention) within previous 6 months
8. History of any significant gastrointestinal, pulmonary or urogenital bleeding, chronic peptic ulcer disease or gastritis
9. Admitting or concomitant diagnosis likely to require major surgery or other invasive procedure within 3 months
10. Major or ophthalmic surgery, biopsy of a parenchymal organ, or serious trauma in the previous 3 months
11. Known history of bronchiectasis
12. End stage renal disease with creatinine clearance <15 ml/min, or requiring dialysis, or likely to require dialysis within 3 months.
13. Previous history of or concurrent intracranial bleeding including hemorrhagic stroke (or clinical presentation consistent with IC bleeding, if CT/MRI not available)
14. History of severe head trauma or trauma within previous 3 months.
15. Known intracranial lesions, including neoplasm, metastatic disease, arterio-venous malformation or aneurysm.

Concomitant conditions

16. Has severe renal insufficiency (i.e. creatinine clearance between ≥ 15 ml/min and < 30 ml/min) and requires a concomitant use of a P-gp inhibitor.
17. Contraindication to anticoagulant therapy (e.g., acquired or inherited bleeding diathesis or coagulopathy, bacterial endocarditis, uncontrolled arterial hypertension [> 200 mmHg systolic or 110 mmHg diastolic] at two successive readings, platelet count < 100,000 mm3 or aPTT > 1.4 x ULN or INR > 1.4, or requirement for thrombolytic therapy), Anemia (Hgb < 10.0/dL) Contraindication to low molecular weight heparins (LMWH)
18. Known abnormality of liver function tests (> 3 x ULN for SGOT/AST, SGPT/ALT or ALP, or > 2 x ULN for total bilirubin in the absence of Gilbert's syndrome), active liver disease or hepatic dysfunction (e.g., cirrhosis)
19. Known HIV infection at screening
20. Concurrent or history of alcohol or drug abuse within 1 year
21. Shock (with systolic BP < 90 mmHg) requiring vasopressors or not responding to simple volume replacement
22. History of hypersensitivity to either of the study articles or any component of their formulations (enoxaparin or betrixaban) including heparin induced thrombocytopenia
23. Pregnancy or breastfeeding or any plan to become pregnant during the study
    Concomitant drugs/procedures:
24. Concomitant dual anti-platelet therapy daily (any 2 of the following: Aspirin, dipyridamole, or any thienopyridine, i.e., clopidogrel, prasugrel, ticlopidine, ticagrelor)
25. Received anticoagulant treatment in the last 14 days more than the amounts listed below:
    A. More than 4 doses of enoxaparin or another low molecular weight heparin
    B. More than 4 doses of fondaparinux
    C. More than 8 doses of unfractionated heparin
    D. An infusion of unfractionated heparin for more than 96 hours or
    E. More than three doses of an oral anticoagulant

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F. Any use of another anti-Factor Xa inhibitor (e.g. rivaroxaban, apixaban) during the current hospitalization

26. > 96 hours of prophylactic use of anticoagulants immediately before beginning study treatment
27. Indication for fibrinolysis or thrombolysis
28. Use of bevacizumab (Avastin®) or similar antiangiogenic therapy within the previous 6 months or planned use during the study period.
29. Concomitant use of mechanical thromboprophylaxis other than graduated compression stockings
30. Use of experimental drugs or devices within previous 30 days at the time of screening

Efficacy Endpoints:

Primary Efficacy Endpoint: The primary composite endpoint is the occurrence of any of the following events through the Day 35 visit:

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

Secondary Efficacy Endpoints:

- Symptomatic VTE: The occurrence of symptomatic VTE through the Day 35 visit (VTE-related death, nonfatal PE or symptomatic DVT)
- The occurrence of asymptomatic proximal DVT, symptomatic DVT (proximal or distal), non-fatal PE, or all-cause mortality through the Day 35 visit

Tertiary and Exploratory Efficacy

The following tertiary and exploratory outcomes were examined. Outcomes 3-6 below are the individual components of the primary outcome.

1. The occurrence of symptomatic DVT (proximal or distal), non-fatal PE, or VTE-related death through the end of parenteral therapy
2. The occurrence of symptomatic DVT (proximal or distal), non-fatal PE, or VTE-related death between the end of parenteral therapy and the Day 35 visit
3. The occurrence of asymptomatic proximal DVT (as detected by ultrasound) through the Day 35 visit
4. The occurrence of symptomatic DVT (proximal or distal) through the Day 35 visit
5. The occurrence of non-fatal PE through the Day 35 visit
6. The occurrence of VTE-related death through the Day 35 visit
7. 35-Day Net Clinical Benefit: The composite of the primary efficacy outcome plus major bleeding through the Day 35 visit
8. 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

All events were adjudicated by the clinical events committee except asymptomatic proximal DVT (as detected by ultrasound) which was determined by the ultrasound core laboratory.

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Safety Endpoints:
Primary Safety Endpoint: The primary safety outcome was the occurrence of major bleeding through 7 days after discontinuation of all study medication. Major bleeding was defined according to International Society of Thrombosis and Hemostasis (ISTH) criteria as follow: Acute, clinically overt (i.e., directly observable), bleeding that was associated with:

- A reduction in hemoglobin of at least 2 g/dL within 48 hours of an overt bleeding event, or
- A transfusion of at least two units of whole blood or red blood cells, or
- A critical area; e.g., intraocular, intracranial, intraspinal, intramuscular with compartment syndrome, retroperitoneal, intra-articular, pericardial, or
- A fatal outcome.

Retinal hemorrhages secondary to diabetic retinopathy or conjunctival bleeds did not qualify as major bleeds.

Secondary Safety Endpoints:

- Clinically relevant non-major bleeding (CRNM bleeding) through 7 days after discontinuation of all study medication
- Major bleeding through the time of parenteral study medication discontinuation
- CRNM bleeding through the time of parenteral study medication discontinuation
- Major bleeding from the time of parenteral study medication discontinuation through Day 35
- CRNM bleeding from the time of parenteral study medication discontinuation through Day 35
- Major bleeding through the time of parenteral study medication discontinuation in patients with severe renal insufficiency (creatinine clearance < 30 ml/min)
- CRNM bleeding through the time of parenteral study medication discontinuation in patients with severe renal insufficiency
- Major bleeding through 7 days after discontinuation of all study medication in patients with severe renal insufficiency
- CRNM bleeding through 7 days after discontinuation of all study medication in patients with severe renal insufficiency
- Stroke, as adjudicated by the CEC

CRNM Bleeding: CRNM bleeding was 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/permanent) cessation of the study treatment, or associated with discomfort for the patient such as pain or impairment of activities of daily life.

Minimal Bleeding: All other reported overt bleeding episodes not meeting the criteria for major or CRNM bleeding were classified as minimal bleeding. Minimal bleeding events were not adjudicated unless associated with a drop in hemoglobin values which met the CEC trigger criteria.

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Adverse Events: Treatment emergent adverse events (TEAEs) were defined as any AE that was not present prior to receiving the first dose of study drug, but which occurred prior to Day 77 of the study, or was present prior to receiving the first dose of study drug but for which the intensity/frequency increased during the study treatment period or prior to Day 77.

Safety Population: The safety population included all patients randomized into the study who received any portion of either study drug.

Clinical Events Committee (CEC):
The following efficacy and safety outcomes was reviewed by an independent adjudication committee: deaths, symptomatic DVT (proximal or distal), non-fatal PE, stroke, major and clinically relevant non major bleeding. All ultrasounds performed per study procedures were submitted to the Central Ultrasound Core Laboratory for determination of asymptomatic proximal DVT. Efficacy and safety outcomes were reviewed after 250, 750, 1500, 3000, 4500 and 7297 patients had completed Visit 3 and data were available for review.

Schedule of Study Events:

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Table 3: Schedule of Study Event:

	Visit 1		Visit 2	Safety	Visit 3	Visit 4
Activity	Screening	Randomization (Day 1)	Day of Discharge [1] (or Day 14 if Hospitalized > 14 days)	Safety FUP [2] (Approximately Day 14 and Day 42)	Day 35 (+7 days)	FUP / EOS [23] (30+5 days following Visit 3)
Obtain Informed Consent	X					
Obtain Pt. ID in IVRS/IWRS	X					
Demographics	X					
Medical & Medication Hx	X [3]					
Physical Examination	X [4]		X		X	
Objective Mobility Assess.	X		X [5]		X	
Vital Signs (BP, T, HR, RR)	X		X		X	
ECG	X [6]		X			
Hematology	X [7]		X [8]		X [8]	
aPTT and PT/INR	X [7]					
Urinalysis [9]	X		X		X	
Serum Pregnancy test [10]	X [7]				X [8]	
C-Reactive Protein	X [8]					
Serum chemistry	X [7]		X [8]		X [8]	
NT-pro BNP (HF pts only)	X [8]		X [8]		X [8]	
Calculation of CrCl		X [11]				
Population PK			X [12]			
D-dimer	X [7, 13]					
Ultrasound Imaging					X [14]	
Assessment of Study Entry Criteria	X	X				
Randomization in IVRS/IWRS		X				
Dispense Study Drug		X [15]	X [15]			
Drug Acct. & Compliance		X	X	X	X	
Betrixaban/placebo Admin.		I	X [16]		X [16]	
Enoxaparin/placebo Admin. [17]		X	X		X	
Outcome Assessments [18]			X	X [20]	X	X
Rankin Assessment [19]			X		X	X
EQOL			X			X
Patient Status Check						X
Con Med Assessment [21]		X	X		X	X
AEs/SAEs Assessment [22]		X	X		X	X

I = Betrixaban/placebo Initial Loading Dose. Patient receives initial loading dose, only on Randomization Day 1, consisting of two 80mg or 40mg betrixaban/placebo capsules.

1. Visit occurred on day of or in the evening prior to hospital discharge and latest on Day 14 if hospitalization is > 14 days.
2. Telephone contact made at the end of parenteral treatment (approximately Day 14) and again 7 days after end of all study drugs (approximately Day 42). Call included discussion of drug accountability (if necessary) and bleeding event outcomes.
3. Medication history obtained in the 2 weeks prior to screening. Relevant medical history reviewed and recorded, including review for additional risk factors.
4. Height and weight to calculate Body Mass Index (BMI) measured.
5. Objective Mobility Assessment performed at Visit 2 and on Day 4 if they did not occur on the same day. Both assessments were performed regardless of Day 4 occurring before or after discharge. If Day 4 occurred after discharge, it could be conducted via telephone call to the patient.
6. Electrocardiograms (ECGs) obtained on admission could be used; there was no requirement for a specific screening ECG.
7. Local lab was used to screen for eligibility: Hgb, platelet count, aPTT, PT/INR, LFTs (SGOT/AST and/or SGPT/ALT, ALP, total bilirubin), creatinine, d-dimer, serum pregnancy test (as applicable). All remaining lab analyses were done through the central lab. Enough blood was drawn to run local and central lab analyses.
8. Test was only sent to the central laboratory for analyses.

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9. Dipstick could be performed in the clinic; if more than trace blood, microscopic urinalysis was required at the local laboratory.
10. Serum Pregnancy testing was only performed in female patients with child bearing potential.
11. Using Cockcroft-Gault Method.
12. Population PK samples were collected and sent to the central laboratory for central coordination and analyses. The exact dates and times of the last 2 doses of betrixaban/placebo were recorded.
13. D-dimer samples at screening were obtained in duplicate for both central and local laboratory analyses and result were available to assess eligibility in patients < 75 years old at randomization.
14. Mandatory routine bilateral lower extremity venous ultrasonography was performed on Day 35 (+ 7 day window) and submitted to the Ultrasound Core Laboratory (EZUS).
15. The need for study drug dose adjustment (D1-D42) was evaluated. A study drug interruption ≤ 7 days was allowed. A loading dose was NOT given to patients restarting study drug.
16. Starting on Day 2, patient received one 80 mg or 40 mg betrixaban/placebo capsule once daily for a total of 35 days (+ 7 day window; i.e., 35 to 42 days of treatment allowed to accommodate Visit 3 scheduling).
17. Starting on Day 1, patients received one SQ injection of either 40 mg or 20 mg enoxaparin/placebo once daily for 10 ± 4 days.
18. Suspected Cases of DVT were evaluated by lower extremity venous ultrasonography or other vascular imaging procedures. Suspected Cases of PE were evaluated by thoracic spiral CT, lung scan with chest x-ray, or pulmonary angiography as per standard of care.
19. Rankin assessment was performed at Visits 2, 3, 4 if the patient experienced a stroke Outcome event.
20. Only assessed for occurrence of major or CRNM bleeding events.
21. Concomitant medications recorded beginning after randomization to study drug through Visit 4/End of Study.
22. AEs recorded beginning after randomization to study drug through Visit 4/End of Study.
23. Visit 4/End of Study could be conducted by telephone.

Source: NDA submission, Module 5.3.5.1, Figure 3, P. 59.

Study Visits:

Patient was screened to determine patient eligibility.
Visit 1 (day of randomization): This visit was planned to occur at randomization while the patient in the hospital once all the screening activities have been conducted and found to meet all eligibility criteria.

Visit 2: This visit was planned to occur on the day of (or in the evening prior to) discharge from the hospital but no later than Day 14 after randomization.

Visit 3: This visit was planned to occur on Day 35 (+ 7 day window, i.e. 35-42 days allowed) after randomization. This visit was planned to be conducted for patients who discontinued betrixaban/betrixaban placebo earlier than the Day 35 due to use of a protocol prohibited medication or any other reason. During visit 3 a mandatory proximal bilateral lower extremity venous ultrasonography was planned to be performed in patients who did not experience a symptomatic VTE.

Visit 4: This visit or telephone call was planned to occur 30 days (+ 5 day window) after the Day 35 visit. Visit 4 planned to perform and document patient status check for safety and symptomatic efficacy outcomes.

Stopping Rules:

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1. Early discontinuation: Any patient requiring interruption of study drug which exceeded seven days was not to be restarted on the study drug. Early discontinuation of study drug could also occur due to the reasons:
    a. Adverse Event
    b. Pregnancy
    c. Abnormal Liver Function Tests (LFTs),
    d. Total Bilirubin ≥ 2 x ULN on any two consecutive occasions in the absence of Gilbert's syndrome
    e. Jaundice
2. Early Termination: Early termination from the study could occur if:
    a. In the opinion of the Investigator, the patient could not safely perform the study procedures required by the protocol. The patient was still followed for safety and symptomatic efficacy events through Visit 4.
    b. The patient decided to withdraw consent from any further study participation for any reason (i.e., discontinued study drug, refused to return for Visit 3 and refused to allow the Investigator to contact them by telephone to obtain clinical follow-up during the Visit 3 and 4 windows). In this case, the specific reason was listed on the eCRF and appropriately documented as such in the patient's source documentation.
    c. Patient died.
    d. Patient was lost to follow-up and the efforts to obtain follow up were appropriately documented as such in the patient's source documentation.
    e. Portola Pharmaceuticals, Inc. terminated the study for any reason.

Sample Size:

The APEX Study was originally powered based on overall population. The sample size of 6850 (3425 patients per treatment group) patients was planned to provide 90% power with 2-sided alpha = 0.01 level or 97.1% power with 2-sided alpha=0.05. The power calculation assumed a control group event rate of 7.5% and a relative reduction of 35% at visit 3 and 25% patients would not be evaluable for the primary efficacy endpoint.

The amendment 3 (June 2014) of the protocol ceased the enrollment of patient with D-dimer values < 2 x ULN and age < 75 years old, and changed the primary efficacy analysis population from overall population to Cohort 1, therefore sample size reassessment was planned to maintain power in Cohort 1 and was planned to be reassessed when approximately 80% (5480) patients have been enrolled to maintain 85% power at 2-sided alpha = 0.01 in cohort 1. The sample size was re-assessed in June 2015. The IDMC meeting minutes (October 13, 2015) included that "There is a 7.98% aggregated event rate, yielding power of 86.9% for 2 sided alpha of 0.01."

Analysis Methods

Analyses of all efficacy outcomes were planned to be conducted via Mantel-Haenszel tests stratified by the two randomization stratification factors: dosing criteria, and entry criteria. All

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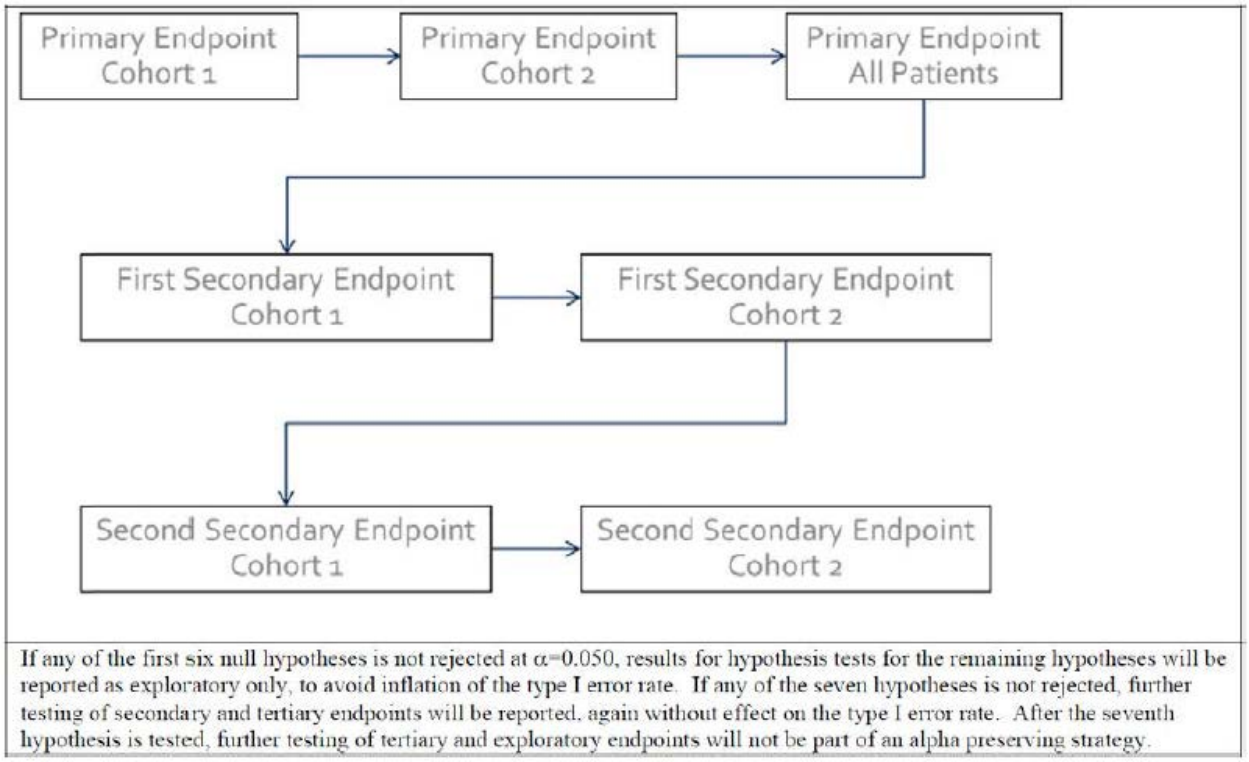
results are presented in terms of relative risk, and all tests on primary and secondary outcomes was performed at 1-sided α =0.025.

All efficacy hypothesis tests were planned to be conducted at 1-sided 0.025 significance level. Betrixaban was compared with enoxaparin through a closed testing, gate-keeping procedure that sequentially tests the primary and secondary efficacy composite outcome hypothesis in each of the cohorts as illustrated in the following figure. If any of these tests are not rejected at the 1-sided 0.025 level, then all remaining tests will cease or all remaining analyses will be considered exploratory.

Figure 3: Graphical Depiction of the Multiple Testing Procedure



Source: NDA submission, Module 5.3.5.1, Figure 4, P. 89.

The tertiary/exploratory efficacy outcomes were to be analyzed, but the analyses would be considered exploratory with all relevant caveats presented.

All safety outcomes, including adverse events and laboratory data will be summarized by treatment and all analyses of safety will be conducted using the safety population. Since there is no adjustment for multiplicity, the analyses of the primary and secondary safety outcomes will be considered descriptive.

Analyses Population:

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Safety Population: The safety population consists of all patients randomized and received any amount of either of the study drugs. All safety analyses were planned to be performed by actual treatment received.

Efficacy Population: The SAP specified that the efficacy analysis population would be Primary Efficacy Outcome Population (PEOP) for the primary efficacy outcome, and First Secondary Efficacy Outcome Population (FSEOP) and Second Secondary Efficacy Outcome Population (SSEOP) for the first and secondary efficacy outcome respectively. PEOP, FSEOP, and SSEOP are subsets of Modified Intent-to-Treat (mITT) population. All efficacy analyses will be performed as randomized.

- PEOP includes all patients in the mITT population who have had assessment of all components of the primary efficacy outcome endpoint which are necessary to determine (via the adjudication process) whether or not a primary efficacy outcome event has occurred.

- FSEOP is the same as the mITT population.

- SSEOP includes all patients in the mITT population who have had assessment of all component of the second secondary efficacy outcome which are necessary to determine (via the adjudication process) whether or not a second secondary efficacy outcome event has occurred.

Interim Analyses

Three interim analyses were planned: (1) one non-binding futility analysis, (2) interim safety analysis, and (3) a sample size reassessment.

1. One non-binding futility analysis was planned when approximately 50% (i.e., approximately 2,568 evaluable patients) of the overall population have evaluable primary outcome data.

2. An interim safety analysis was planned to be performed after 250, 750, 1,500, 3,000, and 4,500 patients have completed Visit 3

3. A sample size reassessment would take place when approximately 80% of the total number of evaluable patients has been enrolled. There would be no opportunity to stop the study for a conclusion of success or futility at the time of the sample size reassessment, only to increase the sample size to maintain at least 85% power at the 1-sided $\alpha = 0.005$ significance level for Cohort 1 of the PEOP.

   No adjustments to the type I error rate will be made to account for the interim analysis or the blinded sample size reassessment, because there is no chance to stop the study early for a conclusion of success with any of these interim analyses.

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Protocol Amendments:

There were four amendments to the original protocol.

Amendment #1:

- Revised the eligibility criteria for patient ≥ 75 years of age to be eligible without the requirement for an ancillary risk factor other than the primary admitting diagnosis and severe immobility.
- Addition was added to Exclusion criterion #3, to exclude patients who are receiving prolonged anticoagulation.
- Addition was added to Exclusion criterion #11, to exclude patients with active lung cancer.
- The exclusion criterion for concomitant use of mechanical thromboprophylaxis was revised to include "sequential compression device" as an exception.
- The use of thrombolytic agents was added as a prohibited medication, with the additional instruction to discontinue study drug if a patient needs to be given a thrombolytic drug.
- Addition of an objective mobility assessment was added to Day 4 for Study patients.

Amendment #2:

- Revised the immobility criteria to allow patients pre-randomization severe immobility to qualify for enrollment, to allow patients with severe immobility to be taken to the hospital room toilet with assistance, and to add the expectation of ongoing, decreased immobility after hospital discharge.
- Modification of Exclusion criterion #20 to allow enrollment of stable, controlled, HIV+ patients
- Modification of Inclusion criterion #5 removed the restriction of the expected duration of the current hospitalization of ≥ 3 days after randomization
- Addition was added to Exclusion criterion #7 to define a lower limit to the permitted body weight - Addition of a Post Randomization Dose Change to allow an adjustment to the initial treatment assignment for patients whose renal function declines
- Clarification to the interim analysis section was added to reflect that the interim analysis is not an interim efficacy analysis

Amendment # 3:

Rationale: The Applicant stated that after enrolling approximately 35% of the anticipated full cohort of patients, D-dimer positive patients were confirmed to be a high risk population based upon pooled blinded aggregate VTE event rates.

- 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

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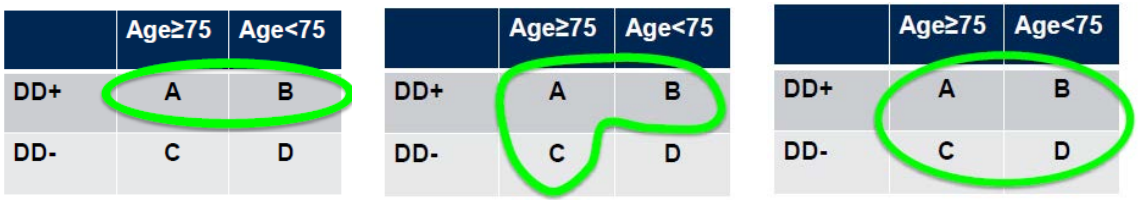
age ≥ 75 years (union). Further enrollment of patients in the biomarker negative subgroup (age <75 and D-dimer <2x ULN) will cease.

- A modification to the primary analysis, testing study cohorts of patients sequentially in the order of anticipated risk of VTE. Patient populations to be analyzed for efficacy include
  - (a) Cohort 1: Primary Patient Population: Patients who have D dimer ≥ 2x ULN at baseline
  - (b) Cohort 2: Patients who have D-dimer ≥ 2x ULN and/or age ≥ 75 years (union).

The following figures illustrate the study population in Cohort 1, Cohort 2, and overall population.

Figure 4: Study Patient Enrichment



Cohort 1 Cohort 2 Overall Population

Protocol amendment 3 stopped the enrollment of patients with D-dimer < 2 ULN and age < 75 years (area D).

- The statistical analysis plan was modified to designate the subgroup of patients with D-dimer ≥ 2 x ULN (previously designated for Subgroup Analyses) as the primary efficacy analysis cohort (Cohort 1). The second analysis population to be tested was patients with D-dimer ≥ 2 x ULN or those ≥ 75 years of age (Cohort 2), and the third analysis was all evaluable patients enrolled in the trial (overall study population), formally if the initial analysis is positive at two-sided significance level of 0.05, and exploratory if not.

- Moved four components of the primary outcome from Tertiary/Exploratory Efficacy Outcomes to Secondary Efficacy Outcomes.

- An addition to the Secondary Safety Outcomes to include “Time to event (days) for a first occurrence of a major bleeding event through 7 days after discontinuation of all study medication” and “Time to event (days) for a first occurrence of a major or CRNM bleeding event through 7 days after discontinuation of all study medication”

- Introduction of a single planned sample size reassessment when approximately 80% of evaluable patients have been enrolled. The Applicant’s decision to perform hierarchical testing of study outcomes starting with the D-dimer positive subgroup (Cohort 1) was

based on the expectation that this population would be enriched for both a greater risk of VTE and a greater benefit of extended duration VTE prophylaxis with betrixaban. It was expected that despite the smaller sample size, the analysis would nonetheless be highly powered to achieve statistical significance due to the higher event rate and larger anticipated treatment benefit in Cohort 1 relative to Cohort 2 (D-dimer positive or age ≥ 75) or the overall study population.

- Modification of Inclusion and Exclusion Criteria:
  - Two additional risk factors are no longer part of the eligibility criteria for those under 75 years of age.
  - The entry criteria continue to require one of the same five medical diagnoses on admission, fulfilling the immobility criteria and one of the following conditions:
    - age ≥ 75 years,
    - a documented D-dimer elevated to ≥ 2x ULN in patients 60-74 years of age, or
    - a documented D-dimer elevated to ≥ 2x ULN in patients 40-59 years of age with a history of VTE or cancer at baseline.
  - The entry criterion for Acute Infection was modified to specify that the patient may present with septic shock but cannot be in septic shock at screening and randomization.
  - The entry criterion for stroke was modified to allow ischemic stroke patients without lower extremity hemiparesis or hemiparalysis as long as the patient satisfies the study immobility criteria.
  - The hemoglobin (Hgb) inclusion criterion has been modified to allow for patients with an Hgb ≥ 9.5 g/dL on two consecutive blood samples on consecutive days to be enrolled if stable or rising, in order to rule out acute active bleed.

Amendment # 4:

- Clarification that the primary efficacy output population (PEOP) will be used for the analysis of the primary endpoint, the first secondary efficacy population (FSEOP) will be used for the analysis of the first secondary endpoint, and the second secondary efficacy output population (SSEOP) will be used for the analysis of the second secondary endpoint
- Specification of day range windows to determine which events are included in the analysis of the primary and secondary endpoints, and of day range windows for compression ultrasound (CUS) to determine which patients are to be included in the analysis of the primary and second secondary endpoints

6 Review of Efficacy

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6.1 Indication

Betrixaban is a factor Xa (FXa) inhibitor proposed for the indication "for extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE."

6.1.1 Methods

One pivotal trial, APEX study (Study 11-019), was conducted to support the proposed indication for extended prophylaxis of VTE in acutely ill medical population with risk factors for VTE.

Please refer to the Section 5.3 for more details of APEX study.

6.1.2 Demographics

A total of 7513 patients were randomized in the APEX Study. The mean age was 76.6 years in the betrixaban arm and 76.2 years in the enoxaparin arm. In both arms approximately two-thirds of the patients randomized were age 75 or older. The majority of patients were women. Patients were predominantly white and majority of patients were severely immobilized. Two-thirds of the patients in both groups had D-dimer of 2 x ULN or above at randomization. Approximately, 23% in the betrixaban group and 21% in the enoxaparin group received reduced dose.

Table 4: Demographic (Efficacy Population)

	Betrixaban (N=3759)	**Enoxaparin (N=3754)**
Age		
Mean age (SD), years	76.6 (8.46)	76.2 (8.39)
Median age (Min, Max), years	77 (40,103)	77 (40,102)
<75 years, n (%)	1184 (32)	1237 (33)
≥ 75 years, n (%)	2575 (68)	2517 (67)
Gender		
Male, n (%)	1705 (45)	1720 (46)
Female, n (%)	2054 (55)	2034 (54)
Race		
White, n (%)	3503 (93)	3518 (94)
Black, n (%)	74 (2)	73 (2)
Asian, n (%)	9 (0.2)	7 (0.2)
Other, n (%)	92 (4.8)	86 (3.8)

Body Mass Index (BMI) at Screening (kg/m²)		
Mean (SD)	29.2 (6.59)	29.5 (6.67)
Median (Min, Max)	28.1 (15.2, 85.3)	28.4 (14.7, 77.3)
Mobility Assessment at screening		
Severe Immobilization, n (%)	3656 (97.3)	3652 (97.3)
Moderate Immobilization, n (%)	95 (2.5)	96 (2.6)
Entry Criteria		
D-dimer ≥ 2 x ULN, n (%)	2341 (62)	2332 (62)
D-dimer < 2 x ULN, n (%)	1382 (37)	1386 (37)
Dosing Reduction Criteria		
Severe renal insufficiency, n (%)	175 (4.7)	150 (4.0)
Receiving concomitant P-Gp only, n (%)	677 (18.0)	649 (17.3)

Source: NDA submission, Module 5.3.5.1, Table 18, P 124-26.

Enrollment by Region:
The vast majority of patients enrolled in APEX trial were from ex-USA, with only 7.0% of all randomized patients from the USA. The enrollment by region was balanced between the two arms with most of subjects from Eastern Europe (~67% of randomized patients).

Table 5: Enrollment by Region and Country–All Randomized Population

Region	**Betrixaban N= 3759**	**Enoxaparin N= 3754**
Western Europe, n (%)	722 (19.2)	628 (16.7)
Eastern Europe, n (%)	2447 (65.1)	2558 (68.1)
Latin America, n (%)	231 (6.1)	237 (6.3)
Asia (Singapore), n (%)	1 (<0.1)	0 (0)
Australia, n (%)	8 (0.2)	12 (0.3)
South Africa, n (%)	58 (1.5)	33 (0.9)
USA/Canada, n (%)	292 (7.8)	286 (7.6)
USA, n (%)	268 (7.1)	259 (6.9)

Source: NDA submission, module 5.3.5.1, Table 10, P. 113.

Medical History:
Medical history at baseline for all randomized patients in APEX trial is summarized by the frequency of baseline disease reported in ≥ 5% of patients using MedDRA preferred term shown in the Table 6 below.

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Table 6: Medical History by Preferred Term in ≥ 5% Patients (All Randomized)

MedDRA Preferred Term	Betrixaban (N=3759)	Enoxaparin (N=3754)
Hypertension, n (%)	2867 (76.3)	2906 (77.4)
Cardiac Failure, n (%)	1027 (27.3)	1048 (27.9)
Chronic Obstructive Pulmonary, n (%)	1026 (27.3)	1014 (27.0)
Myocardial Ischemia, n (%)	782 (20.8)	806 (21.5)
Cardiac Failure Chronic, n (%)	715 (19.0)	711 (18.9)
Diabetes Mellitus, n (%)	702 (18.7)	703 (18.7)
Atrial Fibrillation, n (%)	597 (15.9)	647 (17.2)
Coronary Artery Disease, n (%)	592 (15.7)	606 (16.1)
Obesity, n (%)	535 (14.2)	632 (16.8)
Angina Pectoris, n (%)	515 (13.7)	520 (13.9)
Myocardial Infarction, n (%)	484 (12.9)	483 (12.9)
Osteoarthritis, n (%)	488 (13.0)	477 (12.7)
Pneumonia, n (%)	463 (12.3)	479 (12.8)
Varicose Vein, n (%)	444 (11.8)	459 (12.2)
Type 2 Diabetes Mellitus, n (%)	445 (11.8)	436 (11.6)
Ischemic Stroke, n (%)	419 (11.1)	456 (12.1)
Dyslipidemia, n (%)	383 (10.2)	405 (10.8)
Benign Prostatic Hyperplasia, n (%)	316 (8.4)	329 (8.8)
Renal Failure Chronic, n (%)	327 (8.7)	310 (8.3)
Hyperlipidemia, n (%)	293 (7.8)	318 (8.5)
Depression, n (%)	262 (7.0)	263 (7.0)
Cholecystectomy, n (%)	274 (7.3)	245 (6.5)
Venous Insufficiency, n (%)	241 (6.4)	261 (7.0)
Mitral Valve Incompetence, n (%)	250 (6.7)	239 (6.4)
Essential Hypertension, n (%)	243 (6.5)	242 (6.4)
Cataract, n (%)	239 (6.4)	238 (6.3)
Hypothyroidism, n (%)	235 (6.3)	236 (6.3)
Insomnia, n (%)	216 (5.7)	224 (6.0)
Hypercholesterolemia, n (%)	236 (6.3)	203 (5.4)
Cardiac Failure Congestive, n (%)	234 (6.2)	197 (5.2)
Asthma, n (%)	211 (5.6)	218 (5.8)
Arteriosclerosis, n (%)	202 (5.4)	218 (5.8)
Cholelithiasis, n (%)	197 (5.2)	203 (5.4)
Constipation, n (%)	209 (5.6)	171 (4.6)

Source: NDA submission, module 5.3.5.1, Table 19, P. 128.

Reviewer comments: There were more patients randomized to enoxaparin than betrixaban with clinically relevant medical history at baseline in the following categories:

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- *History of hypertension (2867 [76.3%] in betrixaban vs. 2906 [77.4%] in enoxaparin),*
- *History of myocardial ischemia (782 [20.8%] in betrixaban vs. 806 [21.5%] in enoxaparin),*
- *History of atrial fibrillation (597 [15.9%] in betrixaban vs. 647 [17.2%] in enoxaparin),*
- *Obesity (535 [14.2%] in betrixaban vs. 632 [16.8%] in enoxaparin), and*
- *History of ischemic stroke (419 [11.1%] in betrixaban vs. 456 [12.1%] in enoxaparin).*

However, there were more patients randomized to betrixaban than enoxaparin with clinically relevant medical history at baseline in the following categories:

- *History of hypercholesterolemia (236 [6.3%] in betrixaban vs. 203 [5.4%] in enoxaparin),*
- *History of congestive heart failure (234 [6.2%] in betrixaban vs. 197 [5.2%] in enoxaparin),*

6.1.3 Subject Disposition

Overall there were 8,589 patients screened. There were 1,075 patients recorded as screening failures and 7,514 patients were randomized. The most common reason of screen failure was not meeting the inclusion eligibility criteria (mainly not meeting eligibility criterion for risk factor for age or D-dimer elevation). Since one patient was randomized twice, a total of 7,513 patients were randomized into the study with 3759 patients randomized to the betrixaban group and 3754 patients randomized to the enoxaparin group. A total of 7,441 randomized patients received at least one dose of study drug (3,721 in the betrixaban group and 3,720 in the enoxaparin group) and were included in the mITT population. The mITT population consists of all patients who were adminstered at least one dose of study drug and who have follow-up assessment data on one or more primary or secondary efficacy components. Nine patients did not receive active drug and hence 7,432 were included in the Safety Population (3,716 in the betrixaban group and 3,716 in the enoxaparin group). The Primary Efficacy Outcome Population (PEOP) as defined by the applicant includes all patients in the mITT population who have had assessment of all components of the primary efficacy outcome endpoint which are necessary to determine (via the adjudication process) whether or not a primary efficacy outcome event has occurred.

Disposition of all patients is summarized in Table 7 and Figure 5.

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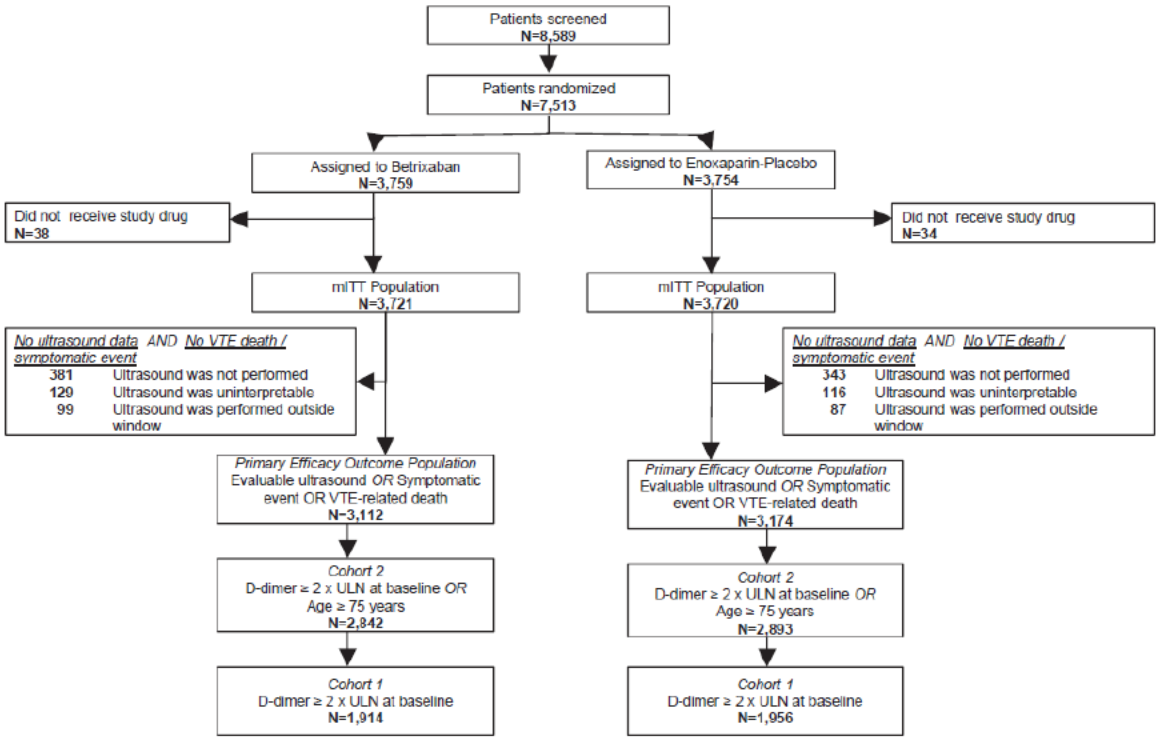
Table 7: Patient Population (All Randomized)

	Betrixaban N (%)	Enoxaparin N (%)	Total N (%)
Randomized	3759 (100)	3754 (100)	7513 (100)
Modified ITT population (randomized and dosed)	3721 (99.0)	3720 (99.1)	7441 (99.0)
Overall Primary efficacy outcome population (PEOP)	3112 (82.8)	3174 (84.5)	6286 (83.7)
Cohort 2 of The PEOP	2842 (75.6)	2893 (77.1)	5735 (76.3)
Cohort 1 of The PEOP	1914 (50.9)	1956 (52.1)	3870 (51.5)
FSEOP of PEOP	3721 (99.0)	3720 (99.1)	7441 (99.0)
SSEOP of PEOP	3245 (86.3)	3310 (88.2)	6555 (87.2)
Safety population (as treated)	3720 (99.0)	3721 (99.1)	7441 (99.0)
Safety population (as reported)	3716 (98.9)	3716 (99.0)	7432 (98.9)

Source: NDA submission, Module 5.3.5.1, Table 14.1.1.1.1, P. 61.

Figure 5: Consort Diagram



*9 patients received only placebo and are excluded from all safety summaries which present data by treatment received; safety population includes 3716 patients for both enoxaparin and betrixaban.
Source: NDA submission, Module 5.3.5.1, Table 14.4.2.28

The proportion of patients who did not complete Visit 4 (study termination Visit and telephone safety and medication assessment follow-up) was comparable between the two groups (7.7% of patients in the betrixaban group and 7.5% of patients in the enoxaparin). However, vital status was later obtained from all those patients.

Table 8: Patient Disposition – Randomized Population

	Betrixaban (N=3759)	**Enoxaparin (N=3754)**
Number of Patients Not Dosed, n (%)	38 (1.0)	34 (0.9)
Number of Patients Dosed, n (%)	3721 (99.0)	3720 (99.1)
Patients Who Completed Visit 4, n (%)	3457 (92.0)	3463 (92.2)
Patients Who Didn't Complete Visit 4, n (%)	289 (7.7)	283 (7.5)
Vital Status Obtained	289 (7.7)	283 (7.5)
Primary Reason For Not Completing Visit 4		
Death, n (%)	206 (5.5)	211 (5.6)
Patient Withdrew Consent, n (%)	43 (1.1)	29 (0.8)
Lost to Follow-Up Originally Recorded, n (%)	11 (0.3)	17 (0.5)
Others, n (%)	29 (0.8)	26 (0.7)

Source: NDA submission, Module 5.3.5.1, modified Tables 13 and 14, P. 188-9.

The reasons for discontinuation are summarized in the Table 9 and Table 33.The percentage of patients discontinuation in the trial was slightly higher in the betrixaban group (18.2%) compared to enoxaparin group (16.6%).

Table 9: Reason for Permanent Discontinuation of Betrixaban/Betrixaban Placebo (Safety Population)

	Betrixaban (N=3716)	**Enoxaparin (N=3716)**
Permanently Discontinued Study Drug, n (%)	678 (18.2)	616 (16.6)
Subjects discontinue study drug due to AEs, n (%)	320 (8.6)	311 (8.4)
Death, n (%)	74 (2.0)	92 (2.5)
Prohibited Medication, n (%)	20 (0.5)	16 (0.4)
Others	264 (7.1)	197 (5.3)

Source: NDA submission, module 5.3.5.1, Table 15, P. 120.

Primary Risk Factors:

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Reasons for hospitalization of the enrolled patients are summarized in Table 10. The most common reason for hospitalization in all randomized patients was acutely decompensated heart failure with similar incidence (45%) in both groups. Patients with acute infection without septic shock, acute respiratory failure, acute ischemic stroke, and acute rheumatic disorders represented 29%, 12%, 11%, and 3.0% of the overall study population, respectively. Approximately half of the patients used anticoagulant prior to randomization. The mean duration of the qualifying hospitalization that led to study entry was 11.4 days, including up to 4 days before randomization allowed per protocol.

Table 10: Primary Risk Factor and Cause of Acute Hospitalization (All Randomized Population)

	Betrixaban (N=3759)	**Enoxaparin (N=3754)**
Cause of the Acute Hospitalization		
Acutely Decompensated Heart Failure, n (%)	1677 (44.6)	1672 (44.5)
Acute Respiratory Failure, n (%)	448 (11.9)	474 (12.6)
Acute Infection Without Septic Shock, n (%)	1112 (29.6)	1058 (28.2)
Acute Rheumatic Disorders, n (%)	109 (2.9)	117 (3.1)
Acute Ischemic Stroke, n (%)	411 (10.9)	432 (11.5)
Anticoagulant Use Prior to Randomization, n (%)	1928 (51.3)	1879 (50)
Duration of Hospitalization at Entry, N	**(N=3684)**	**(N=3697)**
Mean, days (SD)	11.3 (6.4)	11.6 (6.8)
Median, days (Min, Max)	10 (1, 85)	10 (1, 90)

Source: NDA submission, module 5.3.5.1, Table 17, P. 122.

Risk criteria for patients at study entry are summarized in Table 11 and Table 12. Severe immobilization at baseline was reported in similar percentage of patients in the two groups (97.3%). Severe renal insufficiency was present in 4.7% of patients in the betrixaban group and 4.0% of patients in the enoxaparin group. The use of a strong P-gp inhibitor at randomization was reported for 18% of patients in the betrixaban group and 17.3% of patients in the enoxaparin group. The D-dimer level of ≥ 2 x ULN at baseline was present in 62.3% of patients in the betrixaban group and in 62.1% of patients in the enoxaparin group.

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Table 11: Selected Baseline Characteristics of Patients Interest (All Randomized Population)

Reason for dose reduction	Betrixaban (N=3759)	Enoxaparin (N=3754)
Mobility Assessment At Screening		
Severe Immobilization, n (%)	3656 (97.3)	3652 (97.3)
Moderate Immobilization, n (%)	95 (2.5)	96 (2.6)
Missing, n (%)	8 (0.2)	6 (0.1)
Dosing Criteria		
Severe Renal Insufficiency, n (%)	174 (4.7)	150 (4.0)
Strong P-gp Inhibitor, n (%)	677 (18.0)	649 (17.3)
Neither severe Renal Insufficiency nor Concomitant P-Gp Inhibitor, n (%)	2907 (77.3)	2955 (78.7)
Entry Criteria (D-dimer)		
D-dimer ≥ 2 x ULN, n (%)	2341 (62.3)	2332 (62.1)
D-dimer < 2 x ULN, n (%)	1382 (36.8)	1386 (36.9)
Missing, n (%)	36 (1.0)	36 (1.0)

Source: NDA submission, Module 5.3.5.1, Table 17, P#125.

The underlying risk factors were comparable between the two groups. The most frequently reported primary risk criteria were chronic respiratory failure, chronic heart failure and obesity. Treatment groups were balanced for primary risk factors. In both treatment groups, approximately 40% of patients had ≥ 2 additional risk factors.

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Table 12: Risk Criteria (All Randomized Population)

	Betrixaban (N=3759) n (%)	**Enoxaparin (N=3754) n (%)**
History of VTE (DVT or PE)	312 (8.3)	296 (7.9)
Obesity (BMI > 35)	679 (18.1)	734 (19.6)
History of Chronic Venous Insufficiency or Severe Varicose Vein	702 (18.7)	690 (18.4)
Lower Extremity Paresis or Hemiparesis or Hemiparalysis	294 (7.8)	277 (7.4)
Hormone Therapy	43 (1.1)	
History of Cancer	466 (12.4)	443 (11.8)
Chronic Heart Failure (NYHA Class III or IV)	853 (22.7)	865 (23)
Chronic Respiratory Failure	933 (24.8)	893 (23.8)
Active Collagen Vascular Disease with Limited Mobility	93 (2.5)	93 (2.5)
Acute Infection Contributing to Current Hospitalization	602 (16)	620 (16.5)
Concomitant Use of Erythropoiesis Stimulating Agents	4 (0.1)	3 (0.1)
Inherited or Acquired Thrombophilia	3 (0.1)	5 (0.1)
Number of Risk Factors		
0	1007 (26.8)	993 (26.5)
1	1225 (32.6)	1258 (33.5)
2	992 (26.4)	962 (25.6)
3	391 (10.4)	411 (10.9)
4	120 (3.2)	111 (3.0)
≥ 4	24 (0.6)	18 (0.4)

Source: NDA submission, Module 5.3.5.1, Table 17, P#122.

6.1.4 Analysis of Primary Endpoint(s)

Analysis in Cohort 1 of PEOP, Cohort 2 of PEOP, and Overall PEOP

As the pre-specified primary analysis, betrixaban was compared with enoxaparin in Cohort 1 of the PEOP using D-dimer values from the local laboratories. Based on the sponsor's pre-

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specified analysis plan, the event rate of the primary efficacy endpoint was 6.9% in the betrixaban group vs. 8.5% in the enoxaparin group. The relative risk is 0.806 (95% CI [0.647, 1.004]) with p-value of 0.054 from the Cochran–Mantel–Haenszel (CMH) test and the hypothesis test did not reach statistical significance.

The efficacy of betrixaban vs. enoxaparin in Cohort 2 of PEOP and overall PEOP were summarized in the following table. In Cohort 2 of PEOP, the event rate was 5.6% in the betrixaban group vs. 7.1% in the enoxaparin group with relative risk of 0.800 (95% CI [0.655, 0.977]). In the overall PEOP, the event rate was 5.3% in the betrixaban group vs. 7.3% in the enoxaparin group with relative risk of 0.760 (95% CI [0.625, 0.923]).

Table 13: Analysis of Primary Efficacy Endpoint - PEOP

Population	Betrixaban n/N (%)	Enoxaparin n/N (%)	Relative Risk (95% CI)	*p*-Value*
Cohort 1 of PEOP ^	132/1914 (6.9)	166/1956 (8.5)	0.806 (0.647, 1.004)	0.054
Cohort 2 of PEOP #	160/2842 (5.6)	204/2893 (7.1)	0.800 (0.655, 0.977)	
Overall PEOP	165/3112 (5.3)	223/3174 (7.0)	0.760 (0.625, 0.923)	

* Analyses in the cohort 2 of PEOP and overall PEOP were exploratory.
^ Cohort 1of PEOP includes patients with D-dimer ≥ 2 x ULN as determined by the local lab in the PEOP.
# Cohort 2 of PEOP includes patients with D-dimer ≥ 2 x ULN as determined by the local lab or Age ≥ 75 years in the PEOP
Source: Reviewer's Table.

Reviewer Comments:

- *Hierarchical testing and gate keeping procedure were pre-specified in the SAP to control the type I error rate and multiplicity adjustment. Because the hypothesis test in cohort 1 of PEOP did not reach statistical significance, all other analyses are considered exploratory analyses.*

- *Relative risk was smaller in the overall PEOP than in Cohort 2 or cohort 1 of PEOP, indicating that patients not in Cohort 1 or cohort 2 of PEOP benefit most from betrixaban compared with Cohort 1 or cohort 2 of PEOP.*

- *The enriched population (D-dimer ≥ 2 x ULN) may have higher event rates of the primary efficacy endpoint in both arms, D-dimer value may not be an appropriate predictive marker, therefore, the results did not demonstrate more pronounced treatment effect as originally expected in this enriched subgroup.*

Analyses Based on FDA Recommended Efficacy Analysis Population

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During the IND review, the Agency and the sponsor did not resolve the difference in choosing the efficacy analysis population. In the statistical review to respond to the sponsor's submitted SAP (dated 1/29/2016), the statistical reviewer indicated:

"FDA's position on the primary efficacy analysis population mITT, which consists of all randomized patients who have adequate assessment on one or more primary or secondary components, remains unchanged. Also, FDA acknowledges the sponsor's definition of the primary efficacy population which will include all patients in the mITT population who have had assessment of all components of the primary efficacy outcome endpoint which are necessary to determine (via the adjudication process) whether or not a primary efficacy outcome event has occurred.

It appears that the analysis based on FDA's and the sponsor's definition of the analysis population may not agree. If the patients excluded from the mITT population as defined by FDA are only a small group of patients and well balanced between two treatment arms, whether or not to include these patients may not have a great impact on the primary efficacy analysis results. Therefore, FDA considers whether or not to remove these patients from the primary efficacy endpoint analysis as a review issue."

According to this discussion, the efficacy analyses will be analyzed based on both PEOP and mITT populations. The only difference in these two populations is that PEOP population is a subset of mITT and PEOP only includes those patients with all components of the primary efficacy endpoint evaluated, while mITT includes patients who have any assessment of the primary efficacy endpoints.

Since both populations are not ITT population, bias in the results may be introduced as a result of dropping some patients in the analyses. According to the data in the APEX study, number of patients in the mITT population is not very different from the ITT population (only 38 (1%) and 34 (0.9%) of patients were removed from the ITT population for betrixaban and enoxaparin arm, respectively), but the PEOP excluded 17% (647/3759) and 15% (580/3754) of patients from betrixaban and enoxaparin arm, respectively. Therefore, we consider the information in mITT warranted for consideration in interpretation of the results, and the primary efficacy endpoint was further analyzed in mITT population to assess the robustness and consistency of the efficacy results.

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Table 14: Analysis of the Primary Efficacy Endpoint (mITT Population)

Population	Betrixaban n/N (%)	Enoxaparin n/N (%)	Relative Risk (95% CI)
Cohort 1 of mITT ^	132/2314 (5.7)	166/2313 (7.2)	0.791 (0.634, 0.987)
Cohort 2 of mITT #	160/3407 (4.7)	204/3391 (6.0)	0.784 (0.641, 0.959)
Overall mITT	165/3721 (4.4)	223/3720 (6.0)	0.746 (0.613, 0.908)

^ Cohort 1of mITT includes patients with D-dimer ≥ 2 x ULN as determined by the local lab in the mITT population.
# Cohort 2 of mITT includes patients with D-dimer ≥ 2 x ULN as determined by the local lab or Age ≥ 75 years in the mITT population.
Source: Reviewer's Table.

Reviewer's Comments:

- *The estimates of relative risk were smaller and therefore treatment effects looked larger in Cohort 1, Cohort 2, and overall mITT population than in corresponding populations of PEOP. The larger treatment effect estimates in Cohort 1, Cohort 2, and overall mITT populations are due to the larger number of patients included in the denominator in betrixaban arm than in enoxaparin arm, and the number of events stayed the same in the numerator when determining the relative risk in APEX study.*

6.1.5 Analysis of Secondary Endpoints(s)

The first secondary efficacy endpoint was analyzed in Cohort 1 of first secondary efficacy outcome population (FSEOP), Cohort 2 of FSEOP and overall FSEOP. Results were summarized in the following table. Due to the pre-specified hierarchical testing gatekeeping procedure, the analyses were exploratory, and p-values are nominal p-values.

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Table 15: Analysis of First Secondary Efficacy Endpoint - FSEOP

Population	Betrixaban n/N (%)	Enoxaparin n/N (%)	Relative Risk (95% CI)
Cohort 1 of FSEOP ^	30/2314 (1.3)	44/2313 (1.9)	0.674 (0.424, 1.069)
Cohort 2 of FSEOP #	35/3407 (1.0)	49/3391 (1.4)	0.705 (0.458, 1.085)
Overall FSEOP	35/3721 (0.9)	54/3720 (1.5)	0.642 (0.420, 0.980)

^ Cohort 1of FSEOP includes patients with D-dimer ≥ 2 x ULN as determined by the local lab in the FSEOP.
# Cohort 2 of FSEOP includes patients with D-dimer ≥ 2 x ULN as determined by the local lab or Age ≥ 75 years in the FSEOP.
Source: Reviewer's Table.

Second Secondary Efficacy Endpoint

Similarly, the second secondary efficacy endpoint was analyzed in Cohort 1, Cohort 2, and overall second secondary efficacy outcome population (SSEOP) and summarized in Table 16 below. The event rate and relative risk favored betrixaban. However, due to the closed testing, gatekeeping procedure, the analyses was exploratory, and p values are nominal p values.

Table 16: Analysis of Second Secondary Efficacy Endpoint - SSEOP

Population	Betrixaban n/N (%)	Enoxaparin n/N (%)	Relative Risk (95% CI)
Cohort 1 of SSEOP^	232/2014 (11.5)	264/2054 (12.9)	0.889 (0.754, 1.049)
Cohort 2 of SSEOP #	291/2973 (9.8)	329/3018 (10.9)	0.895 (0.771, 1.039)
Overall SSEOP	298/3245 (9.2)	359/3310 (10.8)	0.845 (0.730, 0.978)

^ Cohort 1of SSEOP includes patients with D-dimer ≥ 2 x ULN as determined by the local lab in the FSEOP.
# Cohort 2 of SSEOP includes patients with D-dimer ≥ 2 x ULN as determined by the local lab or Age ≥ 75 years in the FSEOP.
Source: Reviewer's Table.

6.1.6 Other Endpoints

The components of the primary efficacy endpoint were analyzed and are summarized in Table 17 for Cohort 1 of the PEOP. There is one more VTE related death in the betrixaban group than in the enoxaparin group, though the percentages were similar between the two groups. The other three components occurred less frequently in the betrixaban group than the enoxaparin group.

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Table 17: Analysis of Primary Efficacy Endpoint Component – Cohort 1 of PEOP

	Betrixaban (N = 1914)	Enoxaparin (N = 1956)
Primary Efficacy Endpoint, n (%)	132 (6.9)	166 (8.5)
Relative Risk (95% CI)	0.806 (0.647, 1.004)	
p-Value	0.054	
Individual Component		
Asymptomatic Event, n (%)	105 (5.5)	129 (6.6)
Symptomatic DVT, n (%)	14 (0.7)	19 (1.0)
Non-fatal PE, n (%)	5 (0.3)	17 (0.9)
VTE Related Death, n (%)	12 (0.6)	11 (0.6)

Source: Reviewer's Table.

Similarly, the components of the primary efficacy endpoint were analyzed and are summarized in Table 18 for cohort 2 of PEOP. There are same numbers of VTE related death in two groups, while the percentage is higher in the betrixaban group (0.5%) than in the enoxaparin group (0.4%). The other three components occurred less frequently in the betrixaban group than the enoxaparin group.

Table 18: Analysis of Primary Efficacy Endpoint Component – Cohort 2 of PEOP

	Betrixaban (N = 2842)	Enoxaparin (N = 2893)
Primary Efficacy Endpoint, n (%)	160 (5.6)	204 (7.1)
Relative Risk (95% CI)	0.800 (0.655, 0.977)	
Individual Component		
Asymptomatic Event, n (%)	128 (4.5)	162 (5.6)
Symptomatic DVT, n (%)	14 (0.5)	21 (0.7)
Non-fatal PE, n (%)	9 (0.3)	18 (0.6)
VTE Related Death, n (%)	13 (0.5)	13 (0.4)

Source: Reviewer's Table.

Similarly, the component of the primary efficacy endpoint were analyzed and summarized in Table 19 for overall PEOP. All the components occurred less frequently in the betrixaban group than the enoxaparin group.

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Table 19: Analysis of Primary Efficacy Endpoint Component - PEOP

	Betrixaban (N = 3112)	Enoxaparin (N = 3174)
Primary Efficacy Endpoint, n (%)	165 (5.3)	223 (7.0)
Relative Risk (95% CI)	0.760 (0.625, 0.923)	
Individual Component		
Asymptomatic Event, n (%)	133 (4.3)	176 (5.5)
Symptomatic DVT, n (%)	14 (0.4)	22 (0.7)
Non-fatal PE, n (%)	9 (0.3)	18 (0.6)
VTE Related Death, n (%)	13 (0.4)	17 (0.5)

Source: Reviewer's Table.

6.1.7 Subpopulations

The efficacy of betrixaban vs. enoxaparin was analyzed in subgroups of age, gender, race and geographic region of overall PEOP and results are summarized in Table 20.

Table 20: Exploratory Analysis of Primary Efficacy Endpoint in Subgroups of Age, Gender, Race and Geographic Region – Overall PEOP

	Betrixaban n/N (%)	Enoxaparin n/N (%)	Relative Risk (95% CI)
Age			
< 65	12/306 (3.9)	27/334 (8.1)	0.537 (0.284, 1.015)
≥ 65	153/2806 (5.5)	196/2840 (6.9)	0.790 (0.644, 0.970)
< 75	50/974 (5.1)	71/1038 (6.8)	0.770 (0.542, 1.093)
≥ 75	115/2138 (5.4)	152/2136 (7.1)	0.754 (0.596, 0.954)
Gender			
Male	81/1406 (5.8)	102/1447 (7.0)	0.823 (0.620, 1.090)
Female	84/1706 (4.9)	121/1727 (7.0)	0.704 (0.536, 0.923)
Race			
White	150/2915 (5.1)	211/2992 (7.1)	0.737 (0.602, 0.903)
Black or African American	5/53 (9.4)	5/59 (8.5)	0.975 (0.286, 3.321)
Asian	2/7 (28.6)	0/5 (0)	NE (NE, NE)
Multiple	0/21 (0)	1/23 (4.4)	0 (NE, NE)
Other	5/54 (9.3)	3/48 (6.3)	0.796 (0.140, 4.540)
Geographic Region			
North America	12/186 (6.5)	14/196 (7.1)	0.935 (0.455, 1.922)
Non-North America	153/2926 (5.2)	209/3470 (6.0)	0.743 (0.606, 0.910)

Source: Reviewer's Table.

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The efficacy of betrixaban vs. enoxaparin was analyzed in other subgroups of overall PEOP and results are summarized in Table 21.

Table 21: Exploratory Analysis of Primary Efficacy Endpoint in Other Subgroups (Overall PEOP)

	Betrixaban n/N (%)	Enoxaparin n/N (%)	Relative Risk (95% CI)
D-dimer (Local)			
< 2 x ULN	33/1180 (2.8)	55/1204 (4.6)	0.617 (0.403, 0.943)
≥ 2 x ULN	132/1929 (6.8)	167/1968 (8.5)	0.800 (0.642, 0.996)
D-dimer (Central)			
< 2 x ULN	39/1205 (3.2)	51/1260 (4.1)	0.800 (0.530, 1.208)
≥ 2 x ULN	118/1838 (6.4)	165/1822 (9.1)	0.705 (0.561, 0.884)
Belong to Cohort 1 of PEOP			
Yes	132/1914 (6.9)	166/1956 (8.5)	0.806 (0.647, 1.004)
No	33/1186 (2.8)	55/1194 (4.6)	0.618 (0.404, 0.946)
Belong to Cohort 2 of PEOP			
Yes	160/2842 (5.6)	204/2893 (7.1)	0.800 (0.655, 0.977)
No	5/264 (1.9)	18/277 (6.5)	0.291 (0.110, 0.774)
Acutely Decompensated Heart Failure			
Yes	69/1428 (4.8)	83/1481 (5.6)	0.850 (0.623, 1.158)
No	96/1684 (5.7)	140/1693 (8.3)	0.704 (0.547, 0.905)
Acute Respiratory Failure			
Yes	24/353 (6.8)	29/375 (7.7)	0.887 (0.529, 1.488)
No	141/2758 (5.1)	194/2799 (6.9)	0.747 (0.606, 0.922)
Acute Infection without Septic Shock			
Yes	49/883 (5.6)	69 /854 (8.1)	0.717 (0.504, 1.021)
No	116/2228 (5.2)	154/2320 (6.6)	0.781 (0.618, 0.987)
Acute Ischemic Stroke			
Yes	18/353 (5.1)	33/363 (9.1)	0.584 (0.336, 1.016)
No	147/2759 (5.3)	190/2811 (6.8)	0.790 (0.641, 0.973)

Source: NDA Submission, Module 5.3.5.1, Figure 12, P#185, Figure 14, P#186.

No outlier subgroups were identified in the exploratory subgroup analyses.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The efficacy of betrixaban vs. enoxaparin was analyzed by dosing criteria at randomization and actual dose received in the study and is summarized in the following table.

In general, the 80 mg treatment group appears to show favorable results in reduction of VTE events (RR = 0.697 [95% CI: 0.557, 0.872] based on randomized dose and RR = 0.696 [95% CI:

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0.557, 0.869] based on actual dose received). However, no treatment effect was observed in the subgroup of patients who were randomized to receive 40 mg of betrixaban (relative risk = 1.02 [95% CI: 0.68, 1.52]). Similarly, no treatment effect was observed in the subgroup of patients who actually received 40 mg of betrixaban (1.03 [95% CI: 0.68, 1.57]).

Table 22: Exploratory Analysis of Primary Efficacy Endpoint by Dose and Subpopulation - PEOP

	Betrixaban n/N (%)	Enoxaparin n/N (%)	Relative Risk (95% CI)
Dosing Criteria (3 stratum as randomized)			
Severe Renal Insufficiency	12/146 (8.2)	10/110 (9.1)	0.882 (0.400, 1.944)
p-Gp Inhibitor	33/540 (6.1)	33/553 (6.0)	1.064 (0.666, 1.699)
Neither	120/2426 (4.9)	180/2511 (7.2)	0.697 (0.557, 0.872)
Randomized Dose (Combine Stratum "Severe Renal Insufficiency" and "p-Gp Inhibitor")			
80 mg	120/2426 (4.9)	180/2511 (7.2)	0.697 (0.557, 0.872)
40 mg	45/686 (6.6)	43/663 (6.5)	1.015 (0.679, 1.518)
Actual Dose Received			
80 mg	122/2506 (4.9)	181/2562 (7.1)	0.696 (0.557, 0.869)
40 mg	42/603 (7.0)	41/609 (6.7)	1.031 (0.679, 1.570)

Source: Reviewer's Table.

Statistical Comments:

The study population is heterogeneous between the patients who were randomized to receive 80 mg betrixaban (neither have severe renal insufficiency nor receive p-Gp inhibitor) and patients who were randomized to receive 40 mg betrixaban (either have severe renal insufficiency or receive p-Gp inhibitor) (Note, the assignment to reduced dose was not randomized). Therefore, there is not enough evidence from the APEX study to support whether or not 80 mg betrixaban should be recommended to the overall general population. This analysis is exploratory subgroup analysis; therefore interpretation should be taken with caution.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Evaluation of the Treatment Effect During and After the Double-Blind Double Dummy Treatment Period

Due to the concern that the overall results may be driven by the period after the end of parenteral therapy (i.e. double-blind, double dummy period), we conducted exploratory analyses of the symptomatic events that occurrence based on the double-blind double-dummy period 1 (from Randomization through End of Parental Therapy) and after this period 2 (from End of Parental Therapy through 7 days after Study Drug Discontinuation).

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This analysis was based on the symptomatic events only (including Symptomatic DVT, Non-Fatal PE, VTE-Related Death) because asymptomatic DVT component of the primary efficacy endpoint was assessed only at the end of the study within a pre-specified window (Day 32-47) beyond the double-blind, double-dummy period. These analyses were based on data submitted on 2/2/2017 by the applicant in response to the Agency's information request dated 1/26/2017.

The results are shown in the following two tables. Based on the primary analysis population (PEOP), there was no apparent difference between treatments in the incidences of the symptomatic events.

Because the asymptomatic events are not collected at earlier time point (prior to Day 32) and constituted only a small portion of total primary efficacy endpoint events, there are not enough symptomatic events identified for this analyses, therefore, the results cannot support the beneficial effect of Betrixaban over the enoxaparin treatment in earlier time point and over the placebo in later time points based on the analyses of symptomatic events. In addition, because the applicant indicated that asymptomatic DVT component of the primary efficacy endpoint was assessed only at the end of the study within a pre-specified window (Day 32-47), the applicant did not provide sufficient data to support an "extended effect." Therefore, even though the primary analysis results (in Cohort 1, Cohort 2 and PEOP) demonstrated favorable results for betrixaban during 42-day treatment period, it is not clear if the data can support the applicant's claim that betrixaban has an "extended effect."

Table 23: Exploratory Analysis of Symptomatic DVT, Non-Fatal PE, VTE-Related Death from Randomization through End of Parental Therapy

	Betrixaban n/N (%)	**Enoxaparin n/N (%)**	**Risk difference (95% CI)**
Cohort 1 of PEOP^	6/1914 (0.3)	6/1956 (0.3)	-0.01 (-0.34, 0.36)
Cohort 2 of PEOP#	6/2842 (0.3)	9/2893 (0.4)	-0.1 (-0.36, 0.16)
Overall PEOP	6/3112 (0.2)	9/3174 (0.3)	0.09 (-0.15, 0.33)

The analysis includes patients who received the protocol-defined standard duration of enoxaparin/enoxaparin placebo for up to 14 days.
^ Cohort 1of PEOP includes patients with D-dimer ≥ 2 x ULN as determined by the local lab in the PEOP.
# Cohort 2 of PEOP includes patients with D-dimer ≥ 2 x ULN as determined by the local lab and/or Age ≥ 75 years in the PEOP.
Source: Reviewer's Table.

Table 24: Exploratory Analysis of Symptomatic DVT, Non-Fatal PE, VTE-Related Death from End of Parental Therapy through 7 days after Study Drug Discontinuation

Analysis	Betrixaban n/N (%)	Enoxaparin n/N (%)	Risk difference (%) (95% CI)
Cohort 1 of PEOP^	20/1907 (1.1)	33/1947 (1.7)	-0.65 (-1.38, 0.09)
Cohort 2 of PEOP#	23/2834 (0.8)	36/2881 (1.2)	-0.44 (-0.96, 0.09)
Overall PEOP	23/3104 (0.7)	40/3162 (1.3)	-0.52 (-1.02, -0.03)

^ Cohort 1of PEOP includes patients with D-dimer ≥ 2 x ULN as determined by the local lab.
# Cohort 2 of PEOP includes patients with D-dimer ≥ 2 x ULN as determined by the local lab and/or Age ≥ 75 years.
Source: Reviewer's Table.

6.1.10 Additional Efficacy Issues/Analyses

Additional sensitivity analyses were conducted to assess the robustness of the efficacy findings from the primary analysis, and the results are summarized in the following table.

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Table 25: Sensitivity Analysis of Primary Efficacy Endpoint - PEOP

		Betrixaban n/N (%)	Enoxaparin n/N (%)	Relative Risk (95% CI)
Cohort 1 of PEOP				
Per Protocol		102/1636 (6.2)	132/1706 (7.7)	0.803 (0.626, 1.030)
D-dimer from Central Lab		118/1838 (6.4)	165/1822 (9.1)	0.705 (0.561, 0.884)
CUS	**Missing Imputation**	153.7/2314 (6.6)	188.8/2313 (8.2)	0.814 (0.652, 1.015)
	Narrower window (35-42)	132/1818 (7.3)	166/1856 (8.9)	0.807 (0.648, 1.005)
Cohort 2 of PEOP				
Per Protocol		127/2444 (5.2)	165/2538 (6.5)	0.801 (0.640, 1.002)
D-dimer from Central Lab		154/2741 (5.6)	198/2771 (7.1)	0.753 (0.612, 0.926)
CUS	**Missing Imputation**	185.2/34.7 (5.4)	231.1/3391 (6.8)	0.797 (0.652, 0.975)
	Narrower window (35-42)	160/2698 (5.9)	204/2738 (7.5)	0.800 (0.655, 0.976)
Overall PEOP				
Per Protocol		132/2677 (4.9)	180/2791 (6.4)	0.766 (0.616, 0.952)
D-dimer from Central Lab		165/3112 (5.3%)	223/3174 (7.0%)	0.760 (0.625, 0.923)
CUS	**Narrower window (35-42 days)**	165/2957 (5.6%)	223/2995 (7.4%)	0.757 (0.623, 0.920)

Source: NDA Submission, Module 5.3.5.1, Figure 5, P#149, Figure 10, P#170, Figure 11, P#178.

Statistical Comments:

- *Overall, across the various sensitivity analyses, the point estimate of the relative risk were less than one in favor of the betrixaban treatment arm, while the 95% confidence interval of the relative risk crossed one in some analyses, showing the existence of uncertainty of the magnitude of betrixaban treatment effect.*

- *The central laboratory used the commercially available D-dimer test kit (STA-Liatest D-DI), while the local laboratory used different commercial kits and local specifications. In primary analysis (cohort 1 of PEOP), the overall concordance rate between the D-dimer test result from local laboratory and from central laboratory is 80.6%. The applicant calculated Kappa value, which measures the agreement between local and central after*

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accounting for the chance agreement, and Kappa = 0.61, showing a moderate concordance between the local and the central laboratory.

Table 26: Concordance of D-dimer Values by Local vs. Central Lab – mITT Population

	Overall (N=7,175)	Betrixaban (N=3,593)	Enoxaparin (N=3,582)
Local positive/central positive	3,740 (52.13%)	1,894 (52.71%)	1,846 (51.54%)
Local positive/central negative	750 (10.45%)	357 (9.94%)	393 (10.97%)
Local negative/central positive	615 (8.57%)	313 (8.71%)	302 (8.43%)
Local negative/central negative	2,070 (28.85%)	1,029 (28.64%)	1,041 (29.06%)
Stayed the same from local to central	5,810 (80.98%)	2,923 (81.35%)	2,887 (80.60%)
Changed from local positive to central negative	750 (10.45%)	357 (9.94%)	393 (10.97%)
Changed from local negative to central positive	615 (8.57%)	313 (8.71%)	302 (8.43%)

Notes: Patients are classified as positive when D-dimer levels are ≥ 2 x ULN and classified as negative when D-dimer levels are < 2 x ULN. Patients were excluded if they were missing either a local or central lab D-dimer.

Source: NDA Submission, CSR of APEX Study, Table 28, Page # 152.

- *The sensitivity analysis by using narrower CUS windows (35-42 days) led to more missing data for the component of the asymptomatic event of the primary efficacy endpoint, and additional patients were excluded from the analysis population.*

Summary

The applicant submitted a New Drug Application (NDA 208383) for Betrixaban to support the proposed indication "Betrixaban for extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE." The source of the efficacy data consists of a single pivotal Study 11-019 (APEX). The APEX Study was a randomized, double-blind, multinational study. APEX Study was designed to evaluate the extended duration (35 to 42 days) anticoagulation with orally administered betrixaban compared to short duration (6 to 14 days) anticoagulation with subcutaneously administered enoxaparin for prevention of venous thromboembolism (VTE) in hospitalized patients with acute medical illness. Patients were required to be hospitalized for a specified acute medical illness (heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke) for less than 4 days prior to randomization and anticipated to be hospitalized for at least 3 days, and had reduced mobility. In addition, eligible patients needed to have any of the following additional risk factors for VTE:

- ≥ 75 years of age, or
- 60 through 74 years of age with D-dimer ≥ 2 ULN, or
- 40 through 59 years of age with D-dimer ≥ 2 ULN and a history of either VTE or cancer

The primary (composite) outcome was the occurrence of any of the following events through Visit 3 (or up to Day 42):

- Asymptomatic proximal DVT, as detected by ultrasound between Day 32 and Day 47,
- Symptomatic DVT (proximal or distal),
- Non-fatal PE, or
- VTE-related death.

For the primary efficacy endpoint, events were only included if they occurred within a pre-specified day range window approximating the scheduled visit days.

While the study was ongoing (after enrolling 35% of the planned patients), the protocol was amended to enrich the study for population with greater risk for VTE (amendment #3). The eligibility criteria were revised to require the presence of an elevated D-dimer ≥ 2x ULN or age ≥ 75 years as criterion for entry, and also the statistical analysis plan was revised to establish hierarchical testing of study outcomes. As a result two cohorts were established within the overall study population as follows:

- Cohort 1 included patients who had an elevated baseline d-dimer level (i.e., at least two times the upper limit of the normal range)

- Cohort 2 included the patients in cohort 1 plus those who were 75 years of age or older.

The analysis plan was changed by establishing a closed hypothesis testing procedure for the primary efficacy endpoint and designating the subgroup of patients in Cohort 1 as the primary efficacy analysis cohort. A second analysis population to be tested was Cohort 2, and a final analysis was defined as all evaluable patients for every components of the primary endpoint enrolled in the trial. Formally, the subsequent testing would be performed if the analysis of earlier hypothesis test is positive at 1-sided 0.025 significance level and exploratory otherwise.

A total of 7,513 patients were randomized in 1:1 ratio to betrixaban group (n=3759) or enoxaparin group (n=3754). Patients were randomized to receive either:

- Betrixaban: A loading dose of 160 mg betrixaban orally once daily for the first dose and then 80 mg once daily for 35 to 42 days and SQ enoxaparin placebo once daily for 6 to 14 days, or
- Enoxaparin: SQ enoxaparin 40 mg once daily for 6 to 14 days and oral betrixaban placebo once daily for 35 to 42 days.

Patients with severe renal insufficiency (creatinine clearance ≥ 15 and < 30 mL/min) received half of the dose of both study medications (betrixaban 80 mg loading dose, then 40 mg once daily or enoxaparin 20 mg once daily). Patients who took a strong concomitant P-gp inhibitor received a reduced dose of betrixaban (80 mg loading dose, then 40 mg once daily) or enoxaparin 40 mg once daily.

The primary efficacy outcome population (PEOP) was used for all efficacy analyses per statistical analysis plan (SAP). Based on this analysis population (PEOP), a total of 6286 patients (N=3112 for betrixaban and N=3174 for enoxaparin) were included in the PEOP.

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The primary efficacy outcome in Cohort 1 of the PEOP occurred in 132/1914 (6.9%) patients of the betrixaban group and 166/1956 (8.5%) patients of the enoxaparin group, an absolute difference in event rate of 1.6%. The relative risk (RR) was 80.6% (95% CI [0.647, 1.004]). Since the analysis for the primary endpoint in cohort 1 failed to reach statistical significance and based on the statistical analysis plan, the subsequent analyses are considered exploratory.

The RR of the primary efficacy endpoint was 80% (95% CI [0.655, 0.977]) and 76% (95% CI [0.625, 0.923]) for Cohort 2 of PEOP and overall PEOP, respectively.

Several key efficacy review issues are identified which may further complicate the interpretation of the results:

- The population of patients with D-dimer $\geq$ 2 ULN or $\geq$ 75 years old is over sampled in the APEX study compared with general population in practice. Analysis results show heterogeneous efficacy in the enriched population vs. the non-enriched population (i.e. non-Cohort 1 appears to show better treatment effect). Interpretation of the efficacy results may need to take the sub-cohorts of the study population into consideration.

- The description of the study as using active comparator is misrepresentative. The treatment durations in the two treatment arms are not comparable (Betrixaban up to 35±7 days vs. Enoxaparin up to 10 ± 4 days). Also, patients received either SQ enoxaparin or enoxaparin placebo for short period of time (6- 14 days) while oral dosing was continued for the full treatment period duration.

- The occurrence of asymptomatic proximal DVT as detected by ultrasound performed only on or before Day 47. Therefore, the APEX study did not provide sufficient data for adequate assessment of the time course of the treatment effect. The beneficial effect of "extended treatment' (i.e., after discontinuation of enoxaparin at day 6 to 14) cannot be separated from the treatment effect during the 6 to 14 days of enoxaparin active control period. Thus, the sponsor's proposed claim about extended effect can not be confirmed.

Based on exploratory analyses by dose level (40 mg, 80 mg), the 80 mg treatment group appears to show favorable results in reduction of VTE events. However, the assignment of dose levels was determined by baseline risk factor and/or concomitant medication (i.e. severe renal insufficiency; receive strong P-gp) and not by randomized assignment, thus the interpretation of the dose specific analysis results may be confounded by the patient population, therefore there is not enough evidence from the APEX study to support whether or not 80 mg betrixaban should be recommended to the overall general population. This analysis is exploratory subgroup analysis, therefore, the results should be interpreted with caution.

Even though the pre-specified analysis does not meet the pre-specified testing criteria based on Cohort 1, the beneficial effect of betrixaban for Cohort 1 appears to be supported by the results

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based on analyses using the modified ITT population, D-dimer assessment per central laboratory measurement as well as different assessment window for the ultrasound evaluation.

The beneficial effect of betrixaban, appears to also be supported by the results from Cohort 2, PEOP and mITT (modified ITT) population when more patients are included. Furthermore, the subgroup analysis results based on the primary efficacy endpoint for Cohort 1 appear to be consistent. Based on these assessments, this reviewer confirms that betrixaban appears to demonstrate favorable treatment effect based on the reduction of VTE events during 35±7 day treatment period, however, dose effect cannot be fully evaluated due to potential confounding of baseline risk factors and/or concomitant medication, and the actual effect of comparing betrixaban vs. enoxaparin cannot be determined from APEX due to non-comparable treatment duration. Due to these concerns, even though favorable results in betrixaban can be confirmed, the magnitude of the effect is uncertain, so additional results (following the analyses of Cohort 1) are presented descriptively.

7 Review of Safety

7.1 Methods

The review of safety for the proposed indication for extended prophylaxis of venous thromboembolism (VTE) in the acutely ill medical population with risk factors for VTE was primarily based on the safety results from the phase 3 trial, Study 11-019 (APEX). The safety data includes data from all completed phase 2 and 3 clinical studies.

The primary safety data is data from the single pivotal trial Study 11-019 (APEX). APEX trial was a phase 3 designed as an active controlled superiority study to evaluate extended duration (35 to 42 days) anticoagulation with betrixaban compared to enoxaparin given for 6 to 14 days for the prevention of VTE in patients who are at risk due to acute medical illness, immobility, and other VTE risk factors. The study randomized 7,513 patients into two treatment groups, 3,759 in the betrixaban treatment group and 3,754 in the enoxaparin treatment group. Patients who were randomized into the study but did not receive any study drug (72 patients) were excluded from the overall safety population. In addition, 9 patients only received the placebo portion of their randomized treatment assignment were also excluded from the overall safety population. Therefore, the safety population consists of 3716 patients in each treatment arm.

Three supportive phase 2 safety studies were in indications different from the proposed indication of extended thromboprophylaxis in acutely ill medical patients. These trials were conducted in patients with non-valvular atrial fibrillation (PN006, DEC and 08-015, EXPLORE Xa) and in surgical patients after unilateral total knee replacement (Study 05-003, EXPERT).

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1. PN006 (DEC): 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)

2. 08-015 (EXPLORE Xa): A Phase 2, Randomized, Parallel Group, Dose-Finding, Multicenter, 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 in Patients With Non-Valvular Atrial Fibrillation (EXPLORE Xa)

3. 05-003 (EXPERT): Evaluation of the Factor Xa Inhibitor, PRT054021, Against Enoxaparin in a Randomized Trial for the Prevention of Venous Thromboembolic Events After Unilateral Knee Replacement (EXPERT)

In these trials a total of 741 patients were exposed to orally administered betrixaban for at least one dose of 5 to 90 mg and up to 11 months duration.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary betrixaban safety data source was derived from the single pivotal trial APEX (Study 11-019). Additional clinical safety information comes from 20 Phase 1 clinical pharmacology studies and three Phase 2 studies in other indications (one uncontrolled study and two controlled studies).

APEX (Study 11-019)

In the APEX trial, all safety analyses were performed using the overall safety population which consisted of all patients randomized who received any portion of either study drug.

The primary safety endpoint was major bleeding that occurred through 7 days after the last dose of study medication. The key secondary endpoints were the occurrence of clinically relevant non-major bleeding (CRNM bleeding) through 7 days after discontinuation of all study medication and the occurrence of major bleeding through the time of parenteral study medication discontinuation.

The numbers of patients included in the overall Safety Population and Cohorts 1 and 2 of the Safety Population for purposes of the safety analyses presented in this section are as shown below.

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Table 27: 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)

Note: Two patients randomized to betrixaban and one patient randomized to enoxaparin received study drug that included both active betrixaban and double-blind active enoxaparin. For purposes of the safety analyses, these patients are counted in the treatment group to which they were randomized.
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.
Source: NDA submission, Module 5.3.5.1, P. 242.

Of the 3,716 betrixaban-treated patients in the overall safety population, 2,986 (1,827 in Cohort 1; 2,719 in Cohort 2) received 80 mg QD after a single loading dose of 160 mg, and 730 (484 in Cohort 1; 683 in Cohort 2) received 40 mg QD after a single loading dose of 80 mg.

7.1.2 Categorization of Adverse Events

MedDRA terminology version 17.0 was used in the APEX study safety analysis.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The adverse events from clinical trials were pooled in groups based on phases of the study and indication. There were three study groupings: Phase 1 Clinical Pharmacology Studies (most of which contributed to the safety database); Phase 2 Efficacy and Safety Studies in Other Indications (all three Phase 2 studies performed with betrixaban were in indications other than the target indication). Safety results from the pivotal trial (APEX) are presented under 7.2, 7.3, 7.4 and 7.5 below. Safety results from other studies are presented and discussed under section 7.7.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the APEX trial, in the overall safety population (OSP), the median active drug exposure was 36 days in betrixaban group compared to 9 days in enoxaparin group. The mean exposure was 32.7 days in the betrixaban and 9.9 days in the enoxaparin. Approximately 91 % of patients received betrixaban for at least 10 days and ~ 75% received it for at least 35 days.

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Approximately 45% of patients received enoxaparin for up to 10 days and 25% received enoxaparin for up to 14 days. The percentage of patients who reported dose interruption at least once was higher among betrixaban group than that for enoxaparin group 5.0% vs 1.8%. The most common reason for dose interruption was bleeding.

Table 28: Duration of Exposure (Safety Population)

	Betrixaban (N=3716)	**Enoxaparin (N=3716)**
Duration of Active drug Exposure (days)		
Mean (SD) (days)	32.7 (10.87)	9.9 (4.84)
Median (min, max) (days)	36 (1, 54)	9 (1, 45)
At least 1 Day, n (%)	3716 (100)	3716 (100)
At least 3 Days, n (%)	3600 (96.9)	3636 (97.8)
At least 6 Days, n (%)	3490 (93.9)	3423 (92.1)
At least 9 Days, n (%)	3389 (91.2)	1944 (52.3)
At least 10 Days, n (%)	3372 (90.7)	1685 (45.3)
At least 14 Days, n (%)	3295 (88.7)	906 (24.4)
At least 35 Days, n (%)	2763 (74.4)	25 (0.7)
At least 42 Days, n (%)	216 (5.8)	2 (<0.1)
# Patients Reporting Dose Interruptions, n (%)		
1	173 (4.7)	59 (1.6)
2	11 (0.3)	6 (0.2)
3	1 (<0.1)	1 (<0.1)
>3	2 (<0.1)	0
Reason for Interruption, n (%)	187 (5.0)	66 (1.8)
Bleeding, n/N (%)	40 (21)	6 (9)
Others AEs, n/N (%)	58 (31)	20 (30)

Source: NDA submission, Module 5.3.5.1, Table 62, P. 243.

Post-randomization changes in active study drug were low and reported in 46 (1.2%) patients in the betrixaban and 39 (1.0%) of patients in the enoxaparin group. The main reason for post-randomization dose changed was severe renal dysfunction which was reported in 33 (0.9%) patients in the betrixaban arm and 24 (0.6%) patients in the enoxaparin arm.

Reviewer comments: The mean exposure to active study drugs was approximately 3 times longer in the betrixaban group (32.7 days) than in the enoxaparin group (9.9 days). Approximately 5% of patients in the betrixaban and 2% in the enoxaparin had at least one dose interruption. The most common reason for dose interruption in the betrixaban was bleeding.

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7.2.2 Explorations for Dose Response

The betrixaban 80 mg dose once daily for the APEX study was selected based on previous phase 2 studies and dose modeling. The PD modeling of 80 mg QD dose of betrixaban predicted thrombin generation inhibition to be similar to the 2.5 mg BID apixaban used in the ADOPT study (Study of Apixaban for the Prevention of Thrombosis-related Events in Patients With Acute Medical Illness) in acutely ill medical patients as well as to the10 mg QD rivaroxaban[6,7]. Data from phase 1 studies and the phase 2 studies EXPLORE Xa and DEC (PN006) were used to construct a preliminary PK/PD model. The thrombin generation levels in the EXPLORE Xa study were similar between patients with betrixaban concentrations between 12 and 30 ng/mL and patients with therapeutic levels of warfarin (INR 2.0-3.0). The average concentration of betrixaban in EXPLORE Xa for the 80 mg dose was 12 ng/mL, indicating that this concentration should provide similar anticoagulation to warfarin.

A dosing regimen of 40 mg QD of betrixaban for patients who were taking a strong P-gp inhibitor was selected based on two separate phase 1 studies (07-009 and PN010) conducted to evaluate the interaction between strong P-gp inhibitors and betrixaban concentrations because betrixaban is a P-gp substrate. The studies with two strong P-gp inhibitors, ketoconazole and verapamil, both demonstrated a large effect on the PK of betrixaban, leading to the recommendation to reduce betrixaban dose by 50% for co-administration with strong P-gp inhibitors.

A dosing regimen of 40 mg QD of betrixaban for patients with severe renal insufficiency (CrCl ≥ 15 to < 30 mL/min) was selected based on a combined analysis of data from the renal impairment study (08-016) together with patient data from the EXPLORE Xa (08-015) and DEC (PN006) studies. This combined analysis indicated a potential significant increase in betrixaban exposure for patients whose creatinine clearance (CrCl) was lower than 30 mL/min. The results of this study were somewhat equivocal as subjects with normal renal function had clearance levels much higher than those observed previously, while those with mild, moderate, and severe renal impairment showed a modest decline with renal function.

7.2.3 Special Animal and/or In Vitro Testing

In in vitro studies, betrixaban was more stable in human liver microsomes than in either rat or dog liver microsomes. Betrixaban was very stable in liver S9 fractions with estimated half-lives of > 120 minutes when incubated at a final concentration of 1 μM in the S9 fractions obtained from Sprague-Dawley rat, beagle dog, and human livers.

The results of this study demonstrated the ability of recombinant human CYPs to metabolize betrixaban at high concentrations when incubated together.

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7.2.4 Routine Clinical Testing

Routine clinical testing obtained while on the trial included, serum chemistry panel (at Visit 2 Day of discharge or at Day 14 if continue to be hospitalized then Visit 3), hematology and urinalysis (at Visit 2 Day of discharge or at Day 14 if continue to be hospitalized then Visit 3), D-Dimer, aPTT and PT/INR measurement screening and routine bilateral lower extremity venous ultrasonography was performed on Day 35 (+ 7 day window).

7.2.5 Metabolic, Clearance, and Interaction Workup

The predominant pathway of betrixaban metabolism is a non-CYP mediated (NADPH independent) amidolysis. This hydrolysis resulted in the formation of the polar compound, PRT062802 (N,N-dimethyl-4-carboxybenzamidine), which was the only prominent circulating metabolite observed in human plasma and the only prominent metabolite in human urine and feces in the mass balance study. Further studies identified second major metabolite a phase 2 sulfate conjugate metabolite (2-amino-3-(5-chloropyridin-2-yl carbamoyl)-5-methoxyphenyl hydrogen sulfate (PRT063069)). Neither of the metabolites was active and so quantitation was done only to further establish the levels observed in healthy subjects and patients.

Further studies with recombinant CYPs did demonstrate that several CYPs could metabolize betrixaban: 1A1, 1A2, 2B6, 2C9*2, 2C19, 2D6 and 3A4, CYPs 1A1, 1A2, 2B6, 2C9*2, 2D6, and 3A4. Metabolites associated with CYP metabolism did not exceed more than 1% of the total AUC value in the mass balance study, confirming that CYPs do not play a significant role in the metabolism of betrixaban.

In a mass balance study (06-005) the mean total radioactivity recovery was 96%, with 85% excreted into feces, and 11% into urine. Unchanged betrixaban was the predominant component found in human plasma and excreta, accounting for 85.3% of the dose excreted in urine and feces. Excretion of absorbed betrixaban is mostly unchanged through the bile with low renal excretion; approximately 5% of the administered oral dose is found in the urine unchanged. Renal clearance of the absorbed dose has been estimated to be 16% of total clearance.

Oral betrixaban bioavailability of an 80 mg dose was found to be 34% and approximately 60% of betrixaban is protein bound. In studies betrixaban was found to have very little interaction with CYP enzymes at any level and is unlikely to have CYP-mediated drug-drug interaction (DDI). Betrixaban exposure (AUC) increased 2 to 3-fold by co-administration with the strong P-gp inhibitors, verapamil and ketoconazole. Study with non-inhibiting P-gp substrate (digoxin) found that neither betrixaban nor digoxin affected the PK of the other compound. The intended dose of betrixaban is an 80 mg IR capsule for all patients except those patients also taking certain strong P-gp inhibitors for whom the dose will be reduced to 40 mg.

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7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Bleeding: In a recent meta-analysis of the six contemporary randomized clinical trial results using the new oral anticoagulants (NOAC) other than edoxaban: 2 direct thrombin-inhibitors and 4 Factor Xa inhibitors trials, gastrointestinal bleeding was more prominent in the NOAC group vs. warfarin (HR for NOAC: 1.30, 95% CI: 0.97, 1.73)[(6)]. A sex-based meta-analysis also recently documented that bleeding complications occur more frequently in women receiving new oral anticoagulants for VTE than men [(7)]. In addition, two major trials conducted using apixaban (fXa inhibitor) or rivaroxaban (fXa inhibitor) in extended thromboprophylaxis in hospitalized acutely ill medical patients showed that the major safety concern were bleeding.

Liver injury: Hepatotoxicity safety concern has been associated with oral anticoagulant.

Reviewer comments: The applicant appears to have adequately assessed the major safety concerns of bleeding and potential hepatotoxicity associated with similar drugs in this class.

7.3 Major Safety Results

7.3.1 Deaths

A total of 437 deaths were reported in the trial, 220 (5.8%) deaths in betrixaban arm and 217 (5.7%) deaths in the enoxaparin arm. Ten deaths occurred in patients who were randomized but did not receive active study drug. All deaths occurring up to Day 77 were part of a composite efficacy endpoint and were adjudicated by the independent blinded CEC to establish the cause of death. The cause of death was adjudicated for 425 patients with 210 (5.6%) deaths in the betrixaban arm and 215 (5.7%) in the enoxaparin arm. The detailed description of the cause of death is shown in the (Table 29) below.

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Table 29: Adjudicated Cause of Death (All Randomized Population)

	Betrixaban N=3759	Enoxaparin N=3754
Adjudicated Death, All Randomized, n (%)	210 (5.6)	215 (5.7)
Non-Cardiovascular/Infection (Includes Sepsis), n (%)	44 (1.2)	37 (0.5)
Cardiovascular/HF/Cardiogenic shock, n (%)	40 (1.1)	56 (1.5)
Due to Non-Cardiovascular/Pulmonary causes, n (%)	28 (0.7)	24 (0.7)
Other Cardiovascular/Ischemic Stroke, n (%)	24 (0.6)	28 (0.7)
Sudden Death of Unknown Cause, n (%)	16 (0.4)	12 (0.3)
Fatal PE/VTE, n (%)	15 (0.4)	26 (0.7)
Malignancy, n (%)	14 (0.4)	9 (0.2)
Myocardial Infarction, n (%)	11 (0.3)	8 (0.2)
Undetermined Cause of Death, n (%)	8 (0.2)	7 (0.2)
Gastrointestinal (Hepatic and Pancreatic), n (%)	3 (0.1)	0 (0)
Non-Cardiovascular/Other Non-Cardiovascular, n (%)	3 (0.1)	1 (<0.1)
Renal Cause, n (%)	2 (0.1)	3 (0.1)
Fatal Bleeding	1 (<0.1)	1 (<0.1)
Multi-Organ Failure, n (%)	1 (<0.1)	1 (<0.1)
Suicide, n (%)	0 (0)	1 (<0.1)
Other Cardiovascular/Arrhythmic, n (%)	0 (0)	1 (<0.1)

Source: NDA submission, Module 5.3.5.1, Table 92, P. 308.

Of the 437 deaths recorded, 418 (206 [5.5%] in the betrixaban arm and 212 [5.7%] in the enoxaparin arm) were in patients who had a treatment emergent fatal AE. In 12 deaths no fatal TEAE recorded on their CRF and were excluded from the overall safety population. The most common TEAEs leading to death in the betrixaban group were cardiac failure and respiratory failure. The most common TEAEs leading to death in the enoxaparin group were cardiac failure and pneumonia.

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Table 30: Treatment Emergent Adverse Events Leading to Death (Safety Population)

	Betrixaban N=3716	Enoxaparin N=3716
Patient with at least 1 TEAEs Leading to Death, n (%)	206 (5.5)	212 (5.7)
Cardiac Failure[1], n (%)	40 (1.1)	47 (1.3)
Respiratory Failure[2], n (%)	25 (0.7)	12 (0.3)
Pneumonia[3], n (%)	12 (0.3)	17 (0.5)
Sepsis or Septic Shock, n (%)	14 (0.4)	7 (0.2)
Death or Sudden Death, n (%)	12 (0.3)	19 (0.5)
Myocardial Infarction or Ischemia, n (%)	7 (0.2)	7 (0.2)
Cerebrovascular Accident (CVA)[4], n (%)	8 (0.2)	18 (0.5)
Malignancy, n (%)	13 (0.3)	8 (0.2)
Chronic Obstructive Pulmonary Disease, n (%)	8 (0.2)	6 (0.2)
Cardiogenic Shock, n (%)	6 (0.2)	5 (0.2)
Pulmonary Embolism, n (%)	6 (0.2)	10 (0.3)
Sudden Cardiac Death, n (%)	6 (0.2)	5 (0.2)
Brain Edema, n (%)	5 (0.1)	9 (0.2)
Cardiac Arrest, n (%)	5 (0.1)	5 (0.1)
Renal Failure[5], n (%)	2 (<0.1)	4 (0.1)
General Physical Health Deterioration, n (%)	5 (0.1)	1 (<0.1)
Pulmonary Edema, n (%)	3 (0.1)	0 (0)
Multi-Organ Failure, n (%)	0 (0)	6 (0.2)
Intestinal Ischemia, n (%)	2 (<0.1)	0 (0)
Bleeding[6], n (%)	1 (<0.1)	1 (<0.1)
Others, n (%)	26 (0.7)	25 (0.7)

[1] Heart failure includes acute heart failure, chronic heart failure, congestive heart failure and heart failure
[2] Respiratory failure includes acute and chronic respiratory failure and respiratory distress
[3] Pneumonia includes pneumonia, lobar pneumonia, aspiration pneumonia, pulmonary sepsis, pulmonary tuberculosis, respiratory tract infection and staphylococcal pneumonia
[4] Cerebrovascular accident includes ischemic and hemorrhagic stroke, CVA, cerebral infarct
[5] Renal Failure includes acute or chronic renal failure
[6] Fatal bleeding was due to pericardial hemorrhage (betrixaban) and hemorrhage stroke (enoxaparin)
Source: NDA submission, Module 5.3.5.1, Table 93, P. 310.

Reviewer comments: The mortality rate was similar between the two treatment groups at ~ 6%. The rate of TEAEs leading to death was similar between the two groups (5.5% in the betrixaban group vs 5.7% in the enoxaparin group). There were numerical imbalances between the two

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groups in number of deaths due to respiratory failure and ischemic stroke with 25 events of respiratory failure and 6 events of ischemic stroke reported in the betrixaban arm vs 12 events of respiratory failure and 12 events of ischemic stroke reported in the enoxaparin arm.

7.3.2 Nonfatal Serious Adverse Events

The rates of the nonfatal serious adverse events were comparable between the two groups (14.3% in betrixaban vs 12.9% in enoxaparin). The most common nonfatal SAE was serious hemorrhagic nonfatal events followed by heart failure. The rate of serious nonfatal bleed in betrixaban group was two times higher than that in the enoxaparin group (2.4% vs 1.2%). Nonfatal serious heart failure occurred in 2% of patients in the betrixaban group versus 1.6% of patients in the enoxaparin group. There were numerical imbalances in number of patients with nonfatal stroke (14 vs 26 for the betrixaban and enoxaparin, respectively). Ischemic stroke accounted for most of the stroke cases, 13 in the betrixaban group vs. 23 cases in the enoxaparin group. Also there were fewer nonfatal cases of pulmonary embolism in the betrixaban group 5 cases compared to 17 cases in the enoxaparin group. However, there were numerically more patients with malignancies in the betrixaban group compared to enoxaparin group (22 vs. 11).

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Table 31: Nonfatal Serious Adverse Events Reported ≥ 5 patients (Safety Analysis)

	Betrixaban N=3716	Enoxaparin N=3716
Patient with at least one SAE, n (%)	659 (17.7)	617 (16.6)
Patient with at least one SAE Nonfatal, n (%)	533 (14.3)	480 (12.9)
Patient with at least one SAE Nonfatal Related, n (%)	83 (2.2)	49 (1.3)
Hemorrhage[A], n (%)	88 (2.4)	44 (1.2)
Gastrointestinal Hemorrhage, n (%)	18 (0.5)	5 (0.1)
Cardiac Failure[B], n (%)	76 (2.0)	59 (1.6)
Renal Failure[C], n (%)	29 (0.8)	26 (0.7)
Pneumonia, n (%)	45 (1.2)	53 (1.4)
Stroke (Ischemic or Hemorrhagic), n (%)	14 (0.4)	26 (0.7)
Malignancy, n (%)	22 (0.6)	11 (0.3)
Respiratory Failure[D], n (%)	18 (0.5)	17 (0.5)
Pulmonary embolism, n (%)	5 (0.1)	17 (0.5)
Atrial Fibrillation, n (%)	10 (0.3)	23 (0.6)
Myocardial Infarction, n (%)	7 (0.2)	15 (0.4)
Acute myocardial infarction, n (%)	2 (<0.1)	10 (0.3)
Urinary Tract Infection, n (%)	13 (0.4)	11 (0.3)
Coronary Artery Disease, n (%)	8 (0.2)	3 (0.1)
Anemia, n (%)	8 (0.2)	4 (0.2)
Hypotension, n (%)	8 (0.2)	2 (<0.1)
Unstable Angina, n (%)	3 (0.1)	7 (0.2)
Acute Coronary Syndrome, n (%)	6 (0.2)	3 (0.1)
Cerebrovascular Accident	6 (0.2)	3 (0.1)
Sepsis, n (%)	4 (0.1)	5 (0.1)
Atrioventricular Block, n (%)	6 (0.2)	4 (0.1)
Cellulitis, n (%)	3 (0.1)	7 (0.2)
Bronchitis, n (%)	1 (<0.1)	6 (0.2)
Dyspnea, n (%)	6 (0.2)	1 (<0.1)
Dyspnea, n (%)	6 (0.2)	1 (<0.1)
Hepatic Enzyme Increased, n (%)	2 (0.1)	5 (0.1)
Myocardial Ischemia, n (%)	1 (<0.1)	6 (0.2)
Pleural Infusion, n (%)	2 (0.1)	5 (0.1)
Angina Pectoris, n (%)	5(0.1)	0 (0)

[A] Included, hemorrhage, hematoma, hemothorax, hematuria, hemoptysis and epistaxis

[B] Included, cardiac failure, acute and chronic cardiac failure
[C] Included, renal failure, acute and chronic renal failure
[D] Included, respiratory failure, acute and chronic respiratory
Source: NDA submission, Reviewer's Table.

Reviewer comments: The percentages of patients reporting at least one nonfatal SAE in the two groups were comparable (14.3% for betrixaban vs. 12.9% for enoxaparin). However, the rate of nonfatal serious hemorrhagic events reported in the betrixaban group was double the rate of that reported in the enoxaparin group (2.4% vs 1.2%).

7.3.3 Dropouts and/or Discontinuations

In the analysis of the APEX trial, the percentage of patients who permanently discontinued the trial prematurely was slightly higher in the betrixaban arm than that in the enoxaparin arm (18.2% vs 16.6%).

The percentages of patients who discontinued study drug due to adverse events were comparable between the betrixaban (10.3%) and enoxaparin (9.7%) groups. Hemorrhagic events were the most common AEs that led to study drug discontinuation and was reported in 2.4% of patients in the betrixaban arm vs 1.2% in the enoxaparin arm. Adverse events of renal failure or renal impairment, cardiac arrhythmia, cardiac failure, pneumonia were reported with similar occurrences between the two groups. There were fewer patients treated with betrixaban who discontinued treatment due to pulmonary embolism or DVT (16 cases) than among those treated with enoxaparin (27 cases).

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Table 32: Reason for Permanent Discontinuation of Betrixaban/Betrixaban Placebo (Safety Population)

	Betrixaban (N=3716)	Enoxaparin (N=3716)
Permanently Discontinued Study Drug before Visit 3, n (%)	678 (18.2)	616 (16.6)
Patients discontinued study drug due to AEs, n (%)	320 (8.6)	311 (8.3)
Death, n (%)	74 (2.0)	92 (2.5)
Prohibited Medication, n (%)	20 (0.5)	16 (0.4)
Others	264 (7.1)	197 (5.3)
Patients Decision to Stop the Drug, n (%)	115 (3.1)	107 (2.9)
Withdraw Consent, n (%)	33 (0.9)	24 (0.6)
Noncompliance or Lost to Follow-up, n (%)	10 (0.3)	7 (0.2)
Medical Reason, n (%)	14 (0.4)	13 (0.4)
Other Reasons, n (%)	92 (2.5)	46 (1.2)

Source: NDA submission, Module 5.3.5.1, Tables 15, P. 120.

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Table 33: Treatment Emergent Adverse Events Leading to Treatment Discontinuation (Safety Population)

	Betrixaban (N=3716)	Enoxaparin (N=3716)
Patients discontinued study drug due to AEs, n (%)	382 (10.3)	362 (9.7)
Hemorrhage AEs, n (%)	86 (2.3)	37 (1.0)
Renal failure or impairment AEs, n (%)	21 (0.5)	18 (0.5)
Atrial fibrillation or flutter AEs, n (%)	16 (0.4)	28 (0.8)
DVT/PE Adverse Events, n (%)	16 (0.4)	26 (0.6)
Respiratory Failure, n (%)	14 (0.4)	7 (0.2)
Cardiac Failure AEs, n (%)	12 (0.3)	19 (0.5)
Pneumonia AEs, n (%)	11 (0.3)	13 (0.3)
Anemia or Hemoglobin Decreased, n (%)	11 (0.3)	5 (0.1)
Neoplasm, n (%)	11 (0.3)	6 (0.2)
Ischemic Stroke, n (%)	10 (0.3)	11 (0.3)
Chronic obstructive pulmonary disease, n (%)	8 (0.2)	8 (0.2)
Sepsis, n (%)	7 (0.2)	0 (0)
Myocardial Infarction, n (%)	7 (0.2)	9 (0.2)
Abdominal Pain, n (%)	5 (0.1)	3 (0.1)
Other Adverse events, n (%)	147 (4.0))	172 (4.6)

Source: NDA submission, Module 5.3.5.1, Tables 95, P. 320.

Reviewer comments: There were similar percentages of patients who discontinued treatment due to adverse events in both arms. There was an imbalance in number of patients who discontinued treatment due to hemorrhage AEs with double the number in the betrixaban arm (88 cases) than in the enoxaparin arm (44 cases). However, pulmonary embolism and deep venous thrombosis AEs leading to discontinuations of study drug were fewer in the betrixaban arm (16 cases) than that in the enoxaparin arm (27 cases).

7.3.4 Significant Adverse Events

Stroke

Adjudicated stroke events for the overall safety population occurred in 24 (0.65%) patients in the betrixaban group and 41 (1.1%) in the enoxaparin group. The rate of stroke events was higher in the enoxaparin arm than in the betrixaban arm.

Ischemic stroke represented the majority of the reported stroke events among patients in both groups. There were 18 (0.48%) patients in the betrixaban arm and 34 (0.91%) patients in the enoxaparin arm who experienced ischemic stroke. The rate of ischemic stroke events was higher

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in the enoxaparin arm than in the betrixaban arm. The incidences of hemorrhagic stroke and transient ischemic attacks were similar between the two groups. However, there was a numerical imbalance in the number of patients with fatal stroke between the two groups with 7 fatal cases reported in the betrixaban compared to 12 fatal cases in the enoxaparin.

Table 34: Adjudicated Stroke (Safety Population)

	Betrixaban N=3716	**Enoxaparin N=3716**
Subjects with Stroke Events, n (%)	24 (0.65)	41 (1.1)
- Ischemic, n (%)	18 (0.48)	34 (0.91)
- Hemorrhagic	1 (0.03)	1 (0.03)
- Transient Ischemic Attack, n (%)	4 (0.11)	5 (0.13)
- Uncertain Type, n (%)	1 (0.03)	1 (0.03)
Fatal Stroke, n (%)	7 (0.2)	12 (0.3)

Source: NDA submission, Module 5.3.5.1, Table 84, P# 282.

The results of subgroup analyses of adjudicated stroke events for the overall safety population by sex, age, and creatinine clearance were performed by the Applicant and confirmed by the review are presented in Table 35.

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Table 35: Subgroup Analysis of Adjudicated Stroke by sex, age, and creatinine clearance (Safety Population)

	Betrixaban	Enoxaparin
Sex		
Male with Stroke Events, n/N (%)	13/13691 (0.77)	21/1696 (1.24)
Female with Stroke Events, n/N (%)	11/2025 (0.54)	20/2020 (0.99)
Age Groups		
Stroke Events in Age < 65 Years, n/N (%)	5/371 (1.34)	1/395 (0.25)
Stroke Events in Age ≥ 65 Years, n/N (%)	19/3344 (0.57)	40/3321 (1.20)
Stroke Events in Age < 75 Years, n/N (%)	7/1166 (0.60)	10/1226 (0.82)
Stroke Events in Age ≥ 75 Years, n/N (%)	17/2550 (0.67)	31/2490 (1.24)
Creatinine Clearance Local Lab (mL/min)		
Stroke Events in Patient CrCL ≥ 60-<90, n/N (%)	8/1287 (0.62)	13/1338 (0.97)
Stroke Events in Patient CrCL ≥ 30-<60, n/N (%)	12/1582 (0.76)	19/1513 (1.26)
Stroke Events in Patients CrCL < 30, n/N (%)	2/174 (1.15)	2/149 (1.34)

Source: NDA submission, Module 5.3.5.1, Table 85, P# 286.

Reviewer comments: The rate of stroke in patients treated with betrixaban was slightly lower in female (0.54%) than male (0.77%). In patients < 65 years of age, there was a numerically higher stroke event rate in the betrixaban group (1.34%) than in the enoxaparin group (0.25%). The rate of stroke events in patients treated with betrixaban increase with decreasing CrCl (0.6%, 0.8% and 1.2% in mild, moderate and severe renal insufficiency, respectively.

Table 36 shows the subgroup analyses for patients receiving concomitant P-gp inhibitor or aspirin and/or proton inhibitor. In both groups the events rate of stroke were numerically higher in patients who were on strong P-gp inhibitors than in those who were not on strong P-gp inhibitors, and in patients who were on aspirin than those who were not on aspirin. In addition, the rate of stroke events was higher in patients treated with betrixaban and who were on aspirin (0.93%) compared to those who treated with betrixaban and who were not on aspirin (0.29%).

Table 36: Subgroup Analysis of Adjudicated Stroke for Patients (Safety Population)

	Betrixaban	Enoxaparin
Received Strong P-gp Inhibitor	**N=890**	**N=854**
Subjects with Stroke Events, n (%)	8 (0.90)	13 (1.52)
- Ischemic, n (%)	7 (0.79)	11 (1.29)
- Transient Ischemic Attack, n (%)	0 (0.0)	2 (0.23)
Did Not Receive Strong P-gp Inhibitor	**N= 2826**	**N= 2862**
Subjects with Stroke Events, n (%)	16 (0.57)	28 (0.98)
- Ischemic, n (%)	11 (0.39)	23 (.80)
- Transient Ischemic Attack, n (%)	4 (0.14)	3 (0.1)
Took Aspirin and a Proton Pump Inhibitor	**N=1122**	**N=1088**
Subjects with Stroke Events, n (%)	11 (0.98)	16 (1.47)
- Ischemic, n (%)	8 (0.71)	13 (1.19)
- Transient Ischemic Attack, n (%)	2 (0.18)	1 (0.09)
Took Aspirin But not a Proton Pump Inhibitor	**N= 864**	**N= 918**
Subjects with Stroke Events, n (%)	8 (0.9)	11 (1.2)
- Ischemic, n (%)	6 (0.37)	10 (1.1)
- Transient Ischemic Attack, n (%)	1 (0.1)	1 (0.1)
Did Not Take Aspirin During the Study	**N=1730**	**N=1710**
Subjects with Stroke Events, n (%)	5 (0.29)	14 (0.82)
- Ischemic, n (%)	4 (0.23)	11 (0.64)
- Transient Ischemic Attack, n (%)	1 (0.06)	3 (0.18)

Source: NDA submission, Module 5.3.5.1, Tables 14.3.1.18.1 through 14.3.1.18.5, P# 10760-79.

There were 419 patients in the betrixaban arm and 456 patients in the enoxaparin arm who had a history of ischemic stroke at baseline. Among these the number of patients who experienced recurrent ischemic stroke was lower in the betrixaban arm 7/419 (1.7%) than that in the enoxaparin arm 16/456 (3.5%).

Reviewer comments: In general, the rates of ischemic stroke events in the betrixaban group were lower than the enoxaparin group in the subgroup analysis of patients receiving and not receiving concomitant P-gb inhibitor or aspirin or aspirin and/or proton pump inhibitor.

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7.3.5 Submission Specific Primary Safety Concerns

BLEEDING:

Major Bleeding:
The primary safety outcome was the occurrence of major bleeding, defined by reduction in hemoglobin of at least 2 g/dL within 48 hours, a transfusion of at least 2 RBCs units, bleed occurs in critical area or fatal bleed, through 7 days after the last dose of study medication.

The adjudicated primary safety endpoint of major bleeding occurred in 25 (0.67%) patients in the betrixaban arm and in 21 (0.57%) patients in the enoxaparin arm. The rate of major bleeding events in patients who received 80 mg dose of betrixaban or 40 mg of enoxaparin was similar between the two groups at 0.5%. However, among patients who received dose reduction (40 mg betrixaban or 20 mg enoxaparin), there were imbalances in number of patients who reported major bleeding events (10 cases in the betrixaban group vs 5 cases in the enoxaparin group).

Table 37: Adjudicated Major Bleeding Events (Safety Population)

	Betrixaban	**Enoxaparin**
Safety Population	**N=3716**	**N=3716**
Major Bleeding, n (%)	25 (0.57)	21 (0.57)
(95%CI)	(0.41, 0.94)	(0.32, 0.81)
Patient Who Received No dose Reduction	**N=2986**	**N=2991**
Major Bleeding, n/N (%)	15 (0.50)	16 (0.53)
Patient Who Received Dose Reduction, N	**N=730**	**N=725**
Major Bleeding, n/N (%)	10 (1.37)	5 (0.69)

Source: NDA submission, Module 5.3.5.1, Table 70, P. 263.

Fatal Bleeds: There was one fatal bleeding reported in each arm (pericardial bleed in the betrixaban arm and intracranial hemorrhage in the enoxaparin arm).

Major bleeding by location: The most common major bleeding was gastrointestinal (GI) bleeding which occurred in 20 (0.53%) patients in the betrixaban arm and 10 (0.3%) patients in enoxaparin arm. However, intracranial hemorrhage was reported in 2 patients in the betrixaban arm and 7 patients in the enoxaparin arm.

Table 38: Major Bleeding by Site (Overall Safety Population)

Bleeding Site	Betrixaban (N=3716)	Enoxaparin (N=3716)
Gastrointestinal Hemorrhage, n (%)	20 (0.53)	10 (0.3)
Gastrointestinal-Upper	18 (0.5)	7 (0.2)
Gastrointestinal-Lower	2 (<0.1)	3 (0.1)
Non-cardiac Surgical Bleeding, n (%)	0 (0)	1 (<0.1)
Epistaxis	1 (<0.1)	0 (0)
Hematoma Hemorrhage, n (%)	1 (<0.1)	1 (<0.1)
Intracranial Hemorrhage, n (%)	2 (<0.1)	7 (0.2)
Intraocular Hemorrhage, n (%)	0 (0)	1 (<0.1)
Pericardial Hemorrhage, n (%)	1 (<0.1)	1 (<0.1)

Source: NDA Submission, Reviewer's Table.

Subgroup Analyses:
Age And Gender: The subgroup analysis of adjudicated major bleeding events by age (<65 vs ≥65 years, <75 vs ≥75 years) through 7 days after discontinuation of all study medication showed that there were no significant differences in the rates of major bleeding between the two arms. However, the subgroup analysis of adjudicated major bleeding events by gender (male vs female) through 7 days after discontinuation of all study medication suggested that there were significant differences in the rates of major bleeding between the two arms in female patients. Women treated with betrixaban had a greater observed rate of major bleeding events (0.94%) than women treated with enoxaparin (0.40%).

Table 39: Adjudicated Primary Safety Endpoint by Gender and Age (Overall Safety Population)

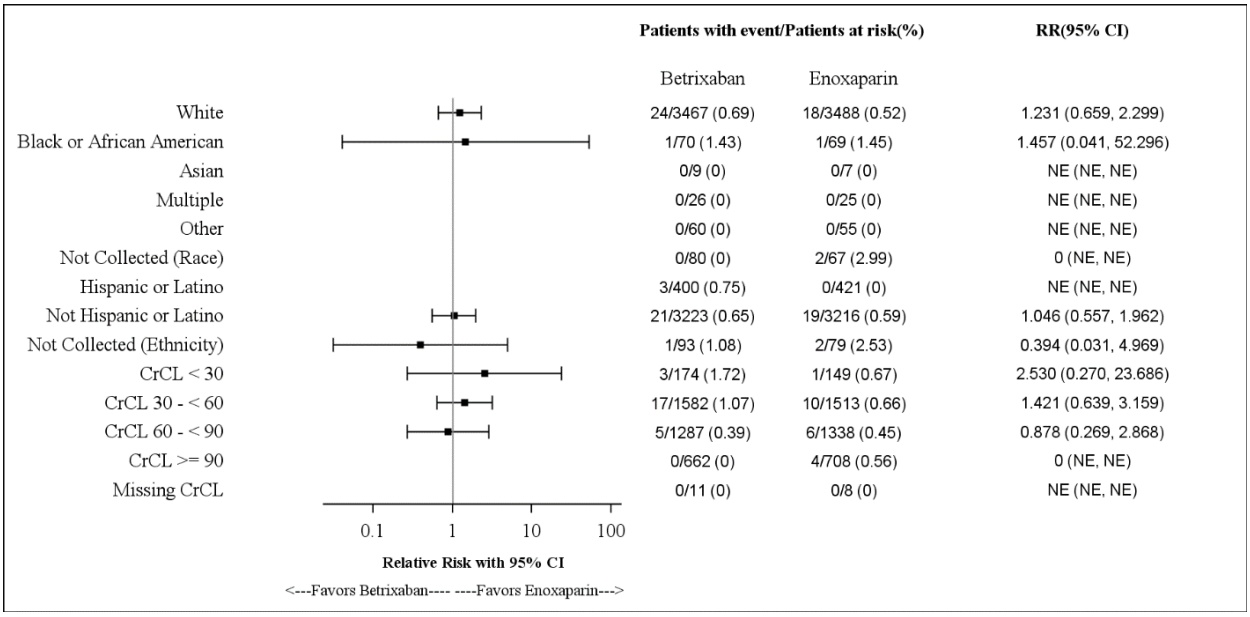
	Betrixaban	Enoxaparin	RR (95% CI)
Male, n/N (%)	6/1691 (0.35)	13/1696 (0.77)	0.39 (0.14, 1.09)
Female, n/N (%)	19/2025 (0.94)	8/2020 (0.40)	2.28 (0.98, 5.27)
<75 years of Age, n/N (%)	3/1166 (0.26)	71/1226 (0.57)	0.45 (0.11, 1.74)
≥75 years of Age, n/N (%)	22/2250 (0.86)	14/2490 (0.56)	1.37 (0.69, 2.72)
<65 years of Age, n/N (%)	0/372 (0)	3/395 (0.76)	0 (NE, NE)
≥65 years of Age, n/N (%)	25/3344 (0.75)	18/3321 (0.54)	1.26 (0.68, 2.33)

RR = Relative Risk, NE = Not evaluable
Source: NDA 208383 submission, 5.3.5.1, Tables 14.3.1.15.5 and 14.3.1.15.6.

Race: Twenty-four of the 25 major bleeding events in the betrixaban group and 18 of the 21 major bleeding events in the enoxaparin group occurred in whites patients.

Creatinine Clearance: There was an increased risk of major bleeding with decreasing creatinine clearance in patients treated with betrixaban (1.7% in CrCl <30, 1.1% in CrCL 30- <60, 0.3% in CrCL ≥ 60) compared with patients treated with enoxaparin (0.7% in CrCl < 30, 0.7% in CrCL 30- <60, 0.5% in CrCL ≥ 60).

Figure 6: Forest Plot of Adjudicated Primary Safety Endpoint by Race, Ethnicity, Creatinine Clearance (Overall Safety Population)



CrCl = Creatinine clearance; Not Collected = Data collection prohibited by regulation; NE = Not evaluable
Note: Only subgroups with total number of patients greater than 10 will be plotted. Baseline creatinine clearance is assessed by the local lab.
Source: NDA 208383 submission, CSR, Figure 23, P#259.

Reviewer comments: In patients who received dose reduction (40 mg of betrixaban or 20 mg enoxaparin) there was a numerical difference in number of patients who experienced major bleeding (10 cases in betrixaban vs 5 cases in enoxaparin). Also, there were numerical imbalances in number of patients who experienced major gastrointestinal (higher in betrixaban) and intracranial hemorrhages (higher in enoxaparin). There were twice as many patients with major GI hemorrhage in the betrixaban arm (20 cases) than that in the enoxaparin arm (10 cases). However, there were fewer patients in betrixaban treated patients who experienced major intracranial hemorrhage than enoxaparin treated patients. Subgroup analyses revealed that

- *There was a higher incidence of major bleeding in women treated with betrixaban compared to women treated with enoxaparin.*
- *The rate of major bleeding in patients treated with betrixaban increased with decreased creatinine clearance.*

Clinically Relevant Non-Major (CRNM) Bleeding:

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Adjudicated CRNM bleeding through 7 days after discontinuation of all study medication in the overall safety population occurred in 91 (2.5%) patients in the betrixaban arm and 38 (1.0%) patients in the enoxaparin arm. The event rate of major or CRNM bleeds was higher in the betrixaban group (3.12%) than in the enoxaparin group (1.59%).

Table 40: Adjudicated Major or CRNM Bleeding Events through Seven Days after Discontinuation of All Study Medication - Safety Population

	Betrixaban N=3716	Enoxaparin N=3716
Major or CRNM Bleeding, n (%) (95%CI)	116 (3.12) (2.56, 3.68)	59 (1.59) (1.19, 1.99)
CRNM Bleeding, n (%)	91 (2.44)	38 (1.02)

Source: NDA Submission, Module 5.3.5.1, Table 14.3.1.2, P. 10487.

Approximately, two thirds of patients with CRNM bleeding in the betrixaban group required cessation of the study drugs. The CRNM bleeding in the betrixaban was mild in 42%, moderate in 46% and severe in 12% of patients. In both groups none of the CRNM bleed was life threatening. Serious bleeding was reported in 46 patients in the betrixaban vs 18 patients in the enoxaparin. Medical intervention was required to manage CRNM bleeding in 38% of patients with the events in the betrixaban group. Hospitalization or prolonged hospitalization required for CRNM bleed for 11 patients in the betrixaban group compared to 8 patients in the enoxaparin patients. The median duration of CRNM bleeding was 3 days in the betrixaban group compared to 2 days in the enoxaparin group. Table 41 summarized the CRNM occurred through seven days after discontinuation of all study drugs.

Table 41: Summary of CRNM Bleeding Events through Seven Days after Discontinuation of All Study Drugs (Safety Population)

	Betrixaban N=3716	Enoxaparin N=3716
CRNM Bleeding, n (%)	91 (2.45)	38 (1.02)
CRNM leading to Discontinuation of Treatment, n (%)	56 (1.5)	24 (0.6)
Bleeding required Medical intervention, n (%)	35 (0.9)	23 (0.6)
CRNM required Hospitalization, n (%)	11 (0.3)	8 (0.2)
Serious CRNM Bleeding, n (%)	45 (1.2)	20 (0.5)
Mild CRNM Bleeding, n (%)	38 (1.0)	17 (0.5)
Moderate CRNM Bleeding, n (%)	42 (1.1)	15 (0.4)
Severe CRNM Bleeding, n (%)	11 (0.3)	6 (0.2)
Median Duration of CRNM Bleeding, Days, (Min, Max)	3 (1, 60)	2 (1, 72)
Patients with at least 3 Days of Bleeding, n (%)	45 (1.2)	17 (0.5)

Source: NDA submission, Module 5.3.5.1, Table 76, P. 269.

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The most frequent CRNM bleeding events were GI hemorrhage, hematuria, epistaxis, and hematoma in both treatment groups. Adjudicated CRNM bleeding per anatomical site are summarized in Table 42.

Table 42: Adjudicated CRNM Bleeding Events by Anatomical Site (Safety Population)

Bleeding Site	Betrixaban (N=3716)	Enoxaparin (N=3716)
Overall CRNM bleeding, n (%)	91 (2.5)	38 (1.0)
Hematuria, n (%)	26 (0.7)	9 (0.2)
Gastrointestinal Hemorrhage, n (%)	28 (0.8)	11 (0.3)
Gastrointestinal-Upper, n (%)	11 (0.3)	4 (0.1)
Gastrointestinal-Lower, n (%)	17 (0.5)	7 (0.2)
Epistaxis, n (%)	15 (0.4)	7 (0.2)
Hematoma, n (%)	8 (0.2)	3 (0.1)
Laceration, n (%)	2 (<0.1)	1 (<0.1)
Hemoptysis, n (%)	3 (0.1)	2 (<0.1)
Vaginal, n (%)	2 (<0.1)	0 (0)
Hemothorax, n (%)	1 (<0.1)	1 (<0.1)
Non-Cardiac Surgical Bleeding, n (%)	1 (<0.1)	0 (0)
Gingival Bleeding, n (%)	0 (0)	1 (<0.1)
Puncture Site, n (%)	0 (0)	1 (<0.1)
Retroperitoneal, n (%)	1 (<0.1)	0 (0)
Others, n (%)	4 (0.1)	2 (<0.1)

Source: NDA 208383 submission, Module 5.3.5.1, Table 75, P. 268.

Subgroup Analyses of Adjudicated Major or CRNM Bleeding:

Subgroup analyses of adjudicated major or CRNM bleeding events through 7 days after discontinuation of all study medication by gender, age and creatinine clearance were performed using overall safety population.

Gender: For males and females, the incidence of major or CRNM bleeds was higher in the betrixaban group than in the enoxaparin group. There was no difference in the event rate between males and females treated with betrixaban (3.19% and 3.06%, respectively).

Age: The subgroup analysis by age groups (< 75 years, ≥75 years, ≥65 years) showed that the incidences of major or CRNM bleeds were higher in the betrixaban group than in the enoxaparin group. The only exception was in the age group of < 65 years of age, there was no apparent difference between the betrixaban group and the enoxaparin group in the incidence of major or CRNM bleeds. The incidence of major or CRNM bleeds was numerically higher in patients ≥ 75

years of age or ≥ 65 years of age than in patients < 75 years of age or < 65 years of age in patients treated with betrixaban.

Creatinine Clearance: The rates of major or CRNM bleeding were lower in the enoxaparin group than in the betrixaban group in each creatinine clearance category. The event rate of major or CRNM bleeding appeared to increase with decreasing creatinine clearance in patients treated with betrixaban.

Concomitant use of Strong P-gp Inhibitors: The incidence of major or CRNM bleeds in the betrixaban group was higher than that in the enoxaparin group in patients taking and not taking P-gp inhibitors. The event rate was numerically higher in patients receiving than in patients not receiving a strong P-gp inhibitor in patients treated with betrixaban. A similar trend was not observed in the enoxaparin group. The incidence of bleeding in patients who received betrixaban 40 mg and were on concomitant P-gp drugs was higher than that in patients who received betrixaban 80 mg dose and were on concomitant P-gp drugs.

Table 43: Subgroup Analysis of Major or CRNM Bleeding (overall safety population)

	Betrixaban (N = 3716)	**Enoxaparin (N = 3716)**
Ag <75 years, n/N (%)	26/1166 (2.2)	20/1226 (1.6)
Ag ≥75 years, n/N (%)	90/2550 (3.5)	39/2490 (1.6)
Ag <65 years, n/N (%)	4/372 (1.1)	5/395 (1.3)
Ag ≥65 years, n/N (%)	112/3344 (3.3)	54/3321 (1.6)
Male, n/N (%)	54/1691 (3.2)	36/1696 (2.1)
Female, n/N (%)	62/2025 (3.1)	23/2020 (1.1)
CrCL ≥ 90 ml/min, n/N (%)	14/662 (2.1)	12/708 (1.7)
CrCL ≥ 60 - < 90 ml/min, n/N (%)	33/1287 (2.6)	15/1338 (1.1)
CrCL ≥ 30 – < 60 ml/min, n/N (%)	60/1582 (3.8)	29/1513 (1.9)
CrCL < 30 ml/min, n/N (%)	9/174 (5.2)	3/149 (2.0)
On P-gp Inhibitor at baseline, n/N (%)	31/691 (4.5)	9/661 (1.4)
No P-gp Inhibitor at baseline, n/N (%)	85/3023 (2.8)	50/3055 (1.6)
Received P-gp Inhibitor and Betrixaban/placebo (80mg), n/N (%)	8/197 (4.1)	2/185 (1.1)
Received P-gp Inhibitor and Betrixaban/placebo (40mg), n/N (%)	23/494 (4.7)	7/476 (1.5)

Source: NDA 208383 submission, Module 5.3.5.1, Tables 14.3.1.15.6, 14.3.1.15.9, 14.3.1.17.1, P#10549, 10585 and 10674.

Reviewer comments: The rate of CRNM bleeding was 2.5 times higher in patients treated with betrixaban compared to those treated with enoxaparin (2.5% vs 1.0%). Also, the event rate of major or CRNM bleeds was higher in the betrixaban group (3.2%) than in the enoxaparin group

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(1.6%). Most common bleeding was GI bleed followed by hematuria. Approximately 60% of the CRNM bleeding events in the betrixaban did not required medical intervention. Serious CRNM bleed was higher among patients in the betrixaban group compared enoxaparin group (1.2% vs 0.5%, respectively). Discontinuation of study drugs was higher in the betrixaban group than in the enoxaparin group (1.5% vs 0.6%, respectively). The median duration of CRNM bleeding was longer in the betrixaban group 3 days than that in the enoxaparin group. The event rate of major or CRNM bleeding appeared to increase with decreasing creatinine clearance and concomitant use of P-gp strong inhibitors in patients treated with betrixaban.

Timing of an Adjudicated Major or CRNM Bleeding Events

Timing of Adjudicated Major or CRNM Bleeding Relative to Administration of Parenteral Medication (i.e., enoxaparin or enoxaparin placebo):
The rate of major or CRNM bleeding was numerically higher in the betrixaban group than in the enoxaparin group through the time of parenteral study medication discontinuation. The rate of major or CRNM bleeding was higher in the betrixaban group from the time of parenteral study medication discontinuation through 7 days after discontinuation of all study medication.

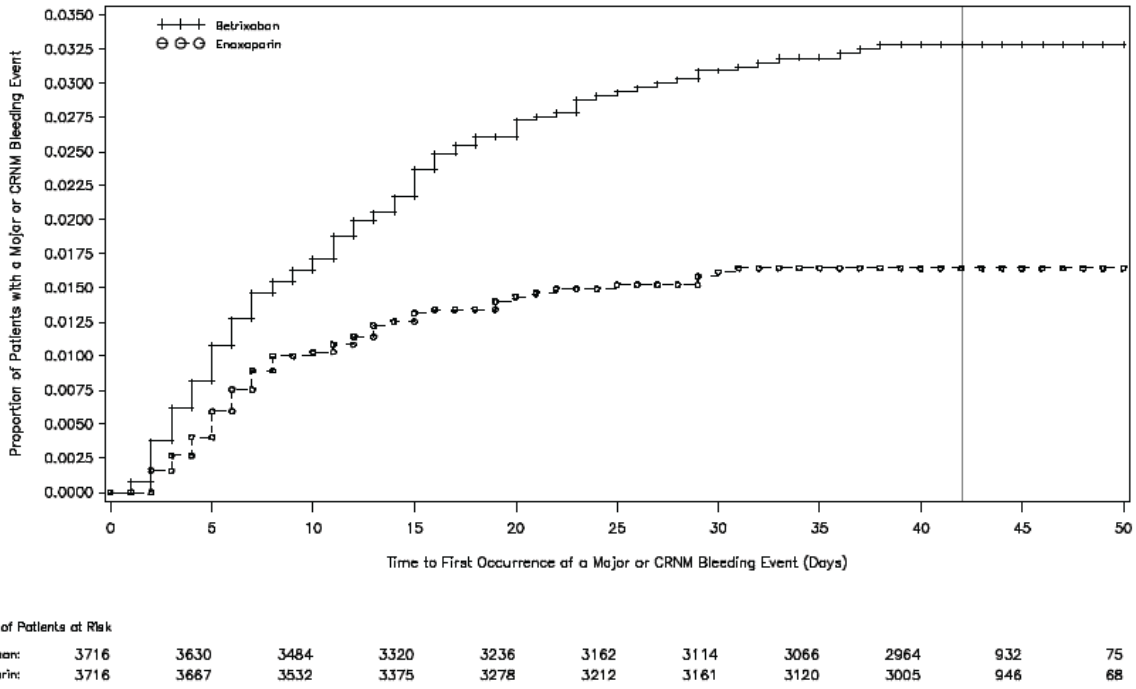
Table 44: Summary of Adjudicated Major or CRNM Bleeding Relative to Administration of Parenteral Medication – Overall Safety Population

	Betrixaban (N = 3716)	***Enoxaparin (N = 3716)***
Through the Time of Parenteral Study Medication Discontinuation		
Patients with Major/CRNM Bleed Events, n (%)	42 (1.13)	27 (0.73)
(95%CI)	(0.79, 1.47)	(0.45, 1.00)
Patients with Major Bleed Events, n (%)	9 (0.24)	9 (0.24)
From Parenteral Study Medication Discontinuation Through 7 Days After All Medication Discontinuation		
Patients with Major/CRNM Bleed Events, n (%)	76 (2.05)	33 (0.89)
(95%CI)	(1.59, 2.50)	(0.59, 1.19)
Patients with Major Bleed Events, n (%)	16 (0.43)	12 (0.32)

Source: NDA 208383 submission, CSR, Table 77, P#273.

Time to First Occurrence of an Adjudicated Major or CRNM Bleeding Event:
There was a significant difference between groups favoring enoxaparin in the time to first occurrence of an adjudicated major or CRNM bleeding event through 7 days after discontinuation of all study medication in the overall safety population shown in Kaplan-Meier Plots below.

Figure 7: Kaplan-Meier Plots for Adjudicated Major or CRNM Bleeding Events through Seven Days after Discontinuation of All Study Medication – Safety Population



Source Data: NDA submission, CSR, Figure 14.3.1.2, P#10488.

Reviewer comments: The analysis of time to bleeding events revealed that there is numerical difference of the rate of major or CRNM bleeding events between the two groups favoring the enoxaparin/placebo group during the time from parenteral drug discontinuation through 7 days after discontinuation of all study medication in the overall safety population. The rate of major or CRNM bleeding events through the time of parental drug discontinuation was higher in the betrixaban group than in the enoxaparin group.

Liver-Related Adverse Events:

There were 162 patients who reported at least one treatment emergent adverse event in the hepatobiliary system, 92 (2.5%) patients in the betrixaban group compared to 72 (1.9%) patients in the enoxaparin group. There were 94 patients who reported liver related adverse events, 54 (1.5%) patients in the betrixaban group and 40 (1.1%) patients in the enoxaparin group. Most of the cases of liver adverse events were mild in severity (38 cases in the betrixaban group and 21 in the enoxaparin group). Serious liver-related events were reported in four patients in the betrixaban group and six patients in the enoxaparin group. Hepatobiliary adverse events are summarized in the following Table 45.

Reference ID: 4076151

Table 45: Treatment Emergent Hepatobiliary Adverse Events – Overall Safety Population

	Betrixaban N= 3716	Enoxaparin N= 3716
Hepatobiliary Disorders, n (%)	92 (2.5)	72 (1.9%)
Cholelithiasis, n (%)	23 (2.5)	24 (1.9)
Hepatic steatosis, n (%)	18 (0.5)	13 (0.3)
Cholecystitis or Cholecystitis chronic, n (%)	18 (0.5)	7 (0.2)
Hepatic cyst, n (%)	11 (0.3)	8 (0.2)
Liver disorder, n (%)	8 (0.2)	9 (0.2)
Hepatomegaly, n (%)	5 (0.1)	1 (<0.1)
Cholecystitis acute, n (%)	4 (0.1)	0
Gallbladder polyp, n (%)	3 (<0.1)	2 (<0.1)
Hyperbilirubinemia, n (%)	2 (<0.1)	1 (<0.1)
Hepatic function abnormal, n (%)	2 (<0.1)	1 (<0.1)
Bile duct stone, n (%)	2 (<0.1)	1 (<0.1)
Portal vein thrombosis, n (%)	1 (<0.1)	0
Non-alcoholic steatohepatitis, n (%)	1 (<0.1)	0
Liver tenderness, n (%)	1 (<0.1)	0
Hepatosplenomegaly, n (%)	1 (<0.1)	0
Hepatocellular injury, n (%)	1 (<0.1)	3 (<0.1)
Hepatitis, n (%)	1 (<0.1)	1 (<0.1)
Hepatic lesion, n (%)	1 (<0.1)	0
Hepatic cirrhosis, n (%)	1 (<0.1)	0
Gallbladder disorder, n (%)	1 (<0.1)	0
Drug-induced liver injury, n (%)	1 (<0.1)	1 (<0.1)
Biliary colic, n (%)	1 (<0.1)	1 (<0.1)
Acute hepatic failure, n (%)	1 (<0.1)	0
Ischemic hepatitis, n (%)	0	1 (<0.1)
Hepatotoxicity, n (%)	0	1 (<0.1)
Hepatic pain, n (%)	0	1 (<0.1)
Cholangitis, n (%)	0	2 (<0.1)

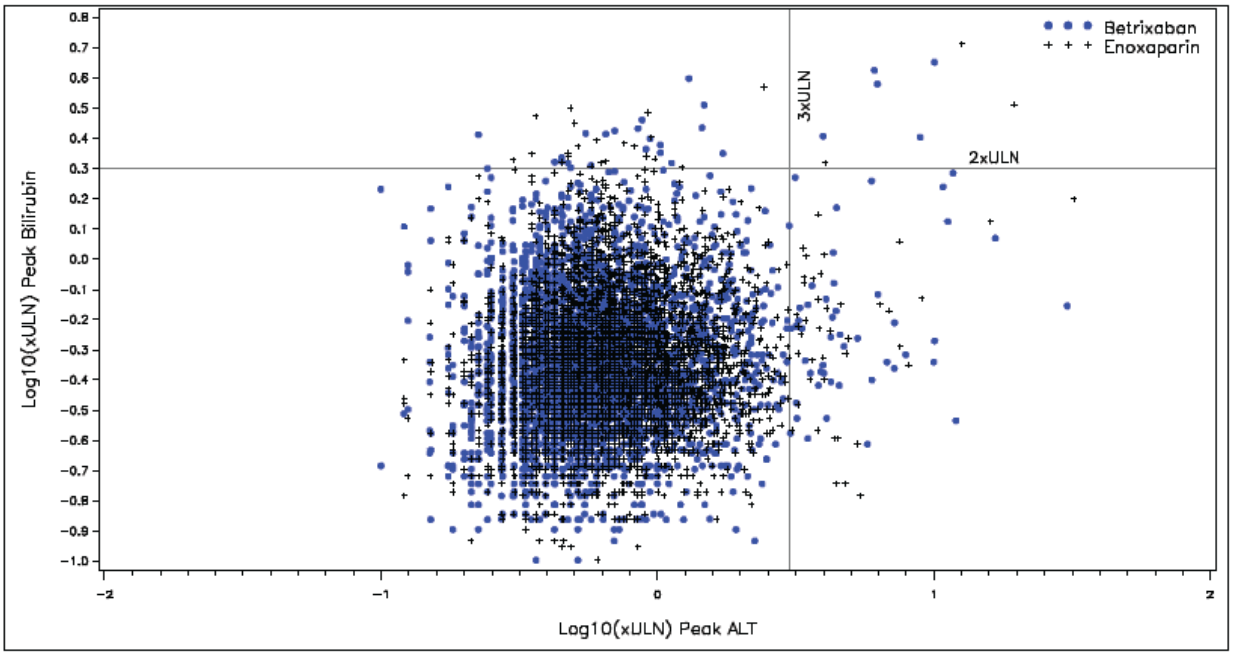
Source: NDA submission, Module 5.3.5.1, Table 100, P. 333.

Abnormal Liver Function Test: The incidences of the event of serum aminotransferase elevations (ALT or AST ≥ 3 times of upper limits of normal [ULN] and ≥5xULN) were comparable between the two groups (1.7% and 0.6% in the betrixaban group and 1.5% and 0.4% in the enoxaparin group, respectively).

The incidence of events of total bilirubin level (TBL) elevations of ≥ 2xULN in the betrixaban group and the enoxaparin group was similar at 0.7% of patients.

To evaluate the potential drug-induced serious hepatotoxicity, an eDISH plot of peak ALT/peak total bilirubin (TBL) was performed (Figure 8 below). A total of 8 cases (5 in the betrixaban and 3 cases in the enoxaparin) were identified in the upper right quadrant of the plot. Of these eight patients, six (4 cases in the betrixaban and 2 cases in the enoxaparin) had ALT or AST > 3 x ULN and Bilirubin > 2 x ULN and ALP < 2 x ULN on the same day.

Figure 8: Post-Baseline Peak Values of Total Bilirubin and ALT – Overall Safety Population



ALT = Alanine aminotransferase; ULN = Upper limit of normal range
Source: NDA submission, Module 5.3.5.1, Figure 26, P 338.

Narratives of the potential Hy's law cases for patients treated with betrixaban [with ALT or AST > 3 x ULN and bilirubin > 2 x ULN and ALP < 2 x ULN] are provided below:

Patient 260060001 was an 81 year old male who was hospitalized for 8 days due to exacerbation of congestive heart failure. He received Clexane for thrombosis prophylaxis for two days prior to randomization. Patients randomized on admission and received betrixaban 80 mg for 13 days. At the time of discharge, he was noted to have an elevation in serum ALT 80 U/L (2 x ULN but other liver tests were within the reference ranges. He discontinued treatment with betrixaban after 13 days for unknown reasons. At the visit 3 assessment (study drug Day 38), he was found to be severely immobilized due to necrotic-hemorrhagic bullous lesion on his hands and legs. His liver enzymes were elevated (ALT 9 x ULN, AST 8 x ULN, and total serum bilirubin 2.5 x ULN mainly direct bilirubin), NT proBNP (1,725 pmol/L) and his ejection fraction was 16%. Ultrasound of the liver suggested no liver pathology. He developed multi-organ failure (acute

liver failure, renal failure and adrenal insufficiency) and died 60 days after starting treatment with study drug (47 days after discontinuing betrixaban treatment). He was treated with multiple antibiotics and amiodarone during the course of his illness.

Patient 320527007 was a 62-year-old male with cardiomyopathy who was hospitalized for decompensated heart failure and was randomized to betrixaban. He received only one day treatment with betrixaban (initial dose of 80 mg since the patient was on amiodarone). His liver chemistries at baseline were elevated (ALT 2.3 x ULN, AST 2.5 x ULN, bilirubin 4 x ULN mostly unconjugated). At study drug day 5 assessment on the day of patient discharge, his liver function tests showed his liver function test continued to rise ALT 8 x ULN, AST 9 x ULN and bilirubin 5 x ULN. Ultrasound of the abdomen showed no hepatobiliary pathology. Patient was not assessed at Visit 3. However, patient assessment on Day 63 of the study drug reported that liver abnormalities was considered resolved.

Patient 620470030 was a 62-year-old male who had coronary artery disease with acutely decompensated heart failure, aortic stenosis, mitral insufficiency, and pulmonary hypertension. He began therapy with betrixaban 80 mg for 6 days. His lab test 1 day after discontinued treatment with betrixaban showed an ALT > 3 x ULN (159 U/L) and a bilirubin > 2 x ULN (42.6 μmol/L). At Visit 3 the patient's ALT was normal (18 U/L) and his bilirubin was only slightly elevated (22.7 μmol/L).

Patient 800044024 was a 79-year-old male with congestive heart failure and atrial fibrillation hospitalized for decompensated heart failure and pneumonia. He was randomized and started on betrixaban 80mg on his second day of hospital admission. Concomitant medications include augmentin for 2 days, trifas and prednisone. He received one dose of enoxaparin 1 day prior enrollment in the study. At the time of discharged from the hospital on day 12 of study drug, his AST and ALT were within normal ranges with increase in total serum bilirubin to ~ 2 x ULN. His liver function tests at the study Visit 3 (Day 39 of the study drug) were found to be abnormal with ALT 6 x ULN, AST 5x ULN, alkaline phosphatase 2.5 x ULN and total serum bilirubin 3.5 x ULN (mainly conjugated). Patient was noted to be cyanotic, tachypneic and his physical exam revealed pedal edema and tachycardia. His NT proBNP was elevated (905.89 pmol/L). At the follow up visit on study drug day 68 the elevated liver functions tested was reported by the investigator as resolved.

Patient 980474153 was an 81-year-old white female who was hospitalized for acute respiratory failure (chronic lung disease) and congestive heart failure (ischemic heart disease). The patient was randomized to the betrixaban received betrixaban 80 mg for 38 days. She received amoxicillin-clavulanate intravenously 3 days prior to treatment with the study drug and concomitantly for up to 13 days. At the Visit 3 (betrixaban day 38), she found to have ALT 4 x ULN, AST 2 x ULN, alkaline phosphatase 1.5 x ULN, and total bilirubin of 3.5 x ULN. Patient liver function tests were within normal range at follow-up 19 days after visit 3.

Reviewer comments: There was no notable difference between the incidence of liver enzymes elevation in patients who received betrixaban and those who received enoxaparin.

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7.4 Supportive Safety Results

7.4.1 Common Adverse Events

APEX TRIAL

Treatment emergent adverse events (TEAEs) were defined as any adverse event (AE) that was not present prior to receiving the first dose of study drug, but which occurred prior to Day 77 of the study, or was present prior to receiving the first dose of study drug but for which the intensity/frequency increased during the study treatment period or prior to Day 77.

The overall incidence of TEAEs in the overall safety population in the betrixaban group (54%) was similar to that in the enoxaparin group (52%). TEAEs considered to be possibly or probably related to treatment were reported in 8.2% of patients for betrixaban vs. 6.2% of patients for enoxaparin. The percentages of patients reporting at least one serious adverse event (SAE) in the two groups were similar (18% for betrixaban vs. 17% for enoxaparin). The rates of severe adverse events were similar between the two groups (12%). TEAEs resulting in death were also reported in a similar percentage of patients in the two groups at 6%.

Table 46: Overall Summary of Treatment Emergent Adverse Events – Safety Population

	Betrixaban N=3716	**Enoxaparin N=3716**
With at Least 1 TEAE, n (%)	2005 (54)	1931 (52)
With at least one TEAE related, n (%)	304 (8)	229 (6)
With at least one SAE, n (%)	657 (18)	615 (17)
With at least one Severe Adverse Events, n (%)	441 (12)	443 (12)
TEAE Leading to Death, n (%)	206 (6)	212 (6)
TEAE Leading to Treatment Discontinuation, n (%)	382 (10)	362 (10)

Source: NDA submission, CSR, Table 87, P.# 292.

The most common TEAEs in the overall safety population in both treatment groups by preferred term were cardiac failure (4.7% in the betrixaban and 4.1% in the enoxaparin) and hypertension (3.7% in the betrixaban and 3.0% in the enoxaparin).

The most frequently reported TEAEs that occurred in at least 1% of patients for the overall Safety population are summarized in Table 47.

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Table 47: Most Frequent TEAEs Reported in > 1% in Either Treatment Group of Overall Safety Population

	Betrixaban N= 3716	Enoxaparin N= 3716
Cardiac Failure (acute or chronic), n (%)	175 (4.7)	151 (4.1)
Hypertension/Hypertensive crisis, n (%)	138 (3.7)	110 (3.0)
Urinary tract infection, n (%)	126 (3.4)	89 (2.4)
Constipation, n (%)	111 (3.0)	101 (2.7)
Hemorrhage, n (%)	110 (3.0)	47 (1.3)
Pneumonia, n (%)	93 (2.5)	113 (3.0)
Hypokalemia, n (%)	93 (2.5)	84 (2.3)
Chronic obstructive pulmonary disease, n (%)	89 (2.4)	81 (2.2)
Insomnia, n (%)	88 (2.4)	89 (2.4)
Renal failure (acute or chronic), n (%)	84 (2.3)	97 (2.6)
Headache, n (%)	74 (2.0)	59 (1.6)
Nausea, n (%)	67 (1.8)	56 (1.5)
Diarrhea, n (%)	64 (1.7)	61 (1.6)
Atrial fibrillation, n (%)	62 (1.7)	106 (2.9)
Hematuria, n (%)	62 (1.7)	28 (0.8)
Cardiac Valve incompetence, n (%)	59 (1.6)	65 (1.8)
Epistaxis, n (%)	58 (1.6)	24 (0.7)
Renal cyst, n (%)	55 (1.5)	47 (1.3)
Anemia, n (%)	53 (1.4)	33 (0.9)
Respiratory failure (acute or chronic) , n (%)	52 (1.4)	36 (1.0)
Deep vein thrombosis, n (%)	46 (1.2)	97 (2.6)
Abdominal pain, n (%)	43 (1.2)	45 (1.2)
Edema peripheral, n (%)	40 (1.1)	19 (0.5)
Ischemic Stroke, n (%)	21 (0.6)	40 (1.1)
Vomiting, n (%)	25 (0.7)	39 (1.1)
Pulmonary embolism, n (%)	15 (0.4)	29 (0.8)

Source: NDA submission, Module 5.3.5.1, Based on Table 88, P. 294.

The incidences of TEAEs for the overall safety population in each system organ class (SOC) are summarized in Table 48. The percentage of patients with at least one TEAE was generally similar in each group for each SOC. Gastrointestinal disorders was the SOC with the highest incidence of TEAEs for the overall betrixaban group (12.5% in the betrixaban group vs. 10.8% in the enoxaparin group) and cardiac disorders was the SOC with the highest incidence for the overall enoxaparin group (12.8% in the betrixaban group vs. 12% in the enoxaparin group).

Table 48: Treatment-Emergent Adverse Events by Decreasing System Organ Class Frequency (Overall Safety Population)

	Betrixaban N= 3716	Enoxaparin N= 3716
Total Number Of TEAEs	4981	4717
Patients with at least 1 TEAE, n (%)	2005 (54.0)	1931 (52.0)
Gastrointestinal Disorders, n (%)	463 (12.5)	401 (10.8)
Infection and Infestations, n (%)	461 (12.4)	471 (12.7)
Cardiac Disorders, n (%)	446 (12.0)	477 (12.8)
Respiratory Disorders, n (%)	365 (9.8)	300 (8.1)
Vascular Disorders, n (%)	326 (8.8)	346 (9.3)
Renal and Urinary Disorders, n (%)	268 (7.2)	220 (5.9)
Nervous System Disorders, n (%)	251 (6.8)	255 (6.9)
Metabolism And Nutrition Disorders, n (%)	231 (6.2)	219 (5.9)
General Disorders, n (%)	194 (5.2)	167 (4.5)
Psychiatric Disorders, n (%)	193 (5.2)	184 (5.0)
Musculoskeletal And Connective Tissue Disorders, n (%)	170 (4.6)	153 (4.1)
Investigations, n (%)	135 (3.6)	140 (3.8)
Skin Disorders, n (%)	100 (2.7)	108 (2.9)
Blood And Lymphatic System Disorders, n (%)	95 (2.6)	81 (2.2)
Injury, Poisoning And Procedural Complications, n (%)	93 (2.5)	80 (2.2)
Hepatobiliary Disorders, n (%)	92 (2.5)	72 (1.9)
Neoplasms, Benign and Malignant, n (%)	74 (2.0)	51 (1.4)
Eye Disorders, n (%)	42 (1.1)	30 (0.8)
Respiratory System Disorders, n (%)	33 (0.9)	21 (0.6)
Endocrine Disorders, n (%)	28 (0.8)	33 (0.9)
Ear Disorders, n (%)	21 (0.6)	19 (0.5)
Surgical and Medical Procedures, n (%)	12 (0.3)	3 (0.1)
Immune System Disorders, n (%)	11 (0.3)	11 (0.3)
Congenital, Familial and Genetic Disorders, n (%)	4 (0.1)	9 (0.2)

Source: NDA submission, module 5.3.5.1, Table 14.3.2.2.3, P. 5106.

TEAE Subgroup Analysis:
Gender: The incidence of TEAE in male and female patients was similar. For the overall safety population TEAEs were reported in 54% of males vs. 54% of females for betrixaban and 51% of males vs. 53% of females for enoxaparin. The percentage of patients with at least one TEAE that was serious was higher in males than in females, overall, but similar within gender for both betrixaban and enoxaparin (20% of males vs. 16% of females for betrixaban and 20% of males vs. 14% of females for enoxaparin).

Age: Overall in betrixaban-treated patients, the percentage of patients with at least one TEAE was greatest in patients ≥ 75 years of age (54.4%) and the least in patients age <65 year (53%).

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The difference in frequency of TEAEs leading to treatment discontinuation between patients ≥ 75 years of age and patients < 65 years of age was 3.2% (11% vs. 7.8%). The difference in frequency of SAEs between patients ≥ 75 years of age and patients < 65 years of age was 2% (18% vs. 16%). In betrixaban-treated patients, the percentage of deaths was higher among patients in ≥65 years age group (5.7%) compared to age group <65 years (4.0%).

Creatinine Clearance: The percentage of patients with at least one TEAE for both the overall betrixaban and enoxaparin groups was greatest in patients with severe renal impairment (61.5% and 58.4%, respectively). Also, the percentage of patients with at least one TEAE leading to discontinuation for both the overall betrixaban and enoxaparin groups was greatest in patients with severe renal impairment (17.8% and 17.4%, respectively).

In patients with severe renal impairment the most frequent TEAE for the betrixaban group overall was hemorrhage (including hematuria) with 14/174 (8%) patients in betrixaban group vs 3/149 (2%) patients in enoxaparin group followed by urinary tract infection which occurred in 12/174 (7%) patients in betrixaban vs. 2/149 (1.3%) patients in enoxaparin.

Reviewer comments: The rate of the TEAEs reported in the betrixaban group (54%) was comparable to the enoxaparin group (52%). The rates of SAEs, TEAEs leading to death and TEAEs leading to discontinuation were similar in the betrixaban groups (18%, 6%, 10%, respectively) and the enoxaparin group (17%, 6%, 10%, respectively). There was a numerical difference in the incidence of hypertensive/hypertensive crisis adverse events (138 events in the betrixaban vs. 110 events in the enoxaparin). The incidence of hemorrhagic events, anemia and peripheral edema were higher in the betrixaban group (3%, 1.4%, 1.1%, respectively) than in the enoxaparin group (1.3%, 0.9%, 0.5%, respectively).

7.4.2 Laboratory Findings

The following laboratory tests were monitored during the trial, liver function test (AST, ALT, bilirubin, alkaline phosphatase, bilirubin), renal function test (creatinine, creatinine clearance, protein in urinalysis, and blood in urinalysis) and hematological test (platelets, leukocytes, hematocrit, hemoglobin) and clinical chemistry (glucose, blood urea nitrogen (BUN), calcium, chloride, creatine kinase, NT proBNP, electrolytes and triglyceride).

Hematological Changes:

- Shift in hemoglobin values from baseline to visit 3: A total of 226 (6.1%) betrixaban-treated patients and 175 (4.7%) enoxaparin-treated patients shifted from normal at baseline to low at visit 3.
- Shift in erythrocytes from baseline to visit 3: A total of 208 (5.6%) betrixaban-treated patients and 134 (3.6%) enoxaparin-treated patients shifted from normal at baseline to low at visit 3.

Serum Chemistry Changes:

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- Shift in blood urea nitrogen value from baseline to visit 3: A total of 442 (11.9%) betrixaban-treated patients and 435 (11.7%) enoxaparin-treated patients shifted from normal at baseline to high at visit 3.
- Shift in triglycerides from baseline to visit 3: A total of 387 (10.4%) betrixaban-treated patients and 368 (9.9%) enoxaparin-treated patients shifted from normal at baseline to high at visit 3.
- Shift in potassium value from baseline to visit 3: A total of 307 (8.3%) betrixaban-treated patients and 365 (9.8%) enoxaparin-treated patients shifted from normal at baseline to high at visit 3.
- Shift in creatinine from baseline to visit 3: A total of 176 (4.7%) betrixaban-treated patients and 140 (3.8%) enoxaparin-treated patients shifted from normal or low at baseline to high at visit 3.
- Shift in creatinine clearance from baseline to visit 3: A total of 235 (6.4%) betrixaban-treated patients and 264 (7.1%) enoxaparin-treated patients shifted from normal or high at baseline to low at visit 3.
- Shift in creatinine kinase from baseline to visit 3: A total of 111 (3.0%) betrixaban-treated patients and 149 (4.1%) enoxaparin-treated patients shifted from normal at baseline to high at visit 3.

Liver function test:

- Shift in aspartate aminotransferase value from baseline to visit 3: A total of 109 (2.9%) betrixaban-treated patients and 105 (2.8%) enoxaparin-treated patients shifted from normal at baseline to high at visit 3.
- Shift in alanine aminotransferase value from baseline to visit 3: A total of 128 (3.4%) betrixaban-treated patients and 138 (3.7%) enoxaparin-treated patients shifted from normal or low at baseline to high at visit 3.
- Shift in alkaline phosphatase value from baseline to visit 3: A total of 222 (6.0%) betrixaban-treated patients and 222 (6.0%) enoxaparin-treated patients shifted from normal at baseline to high at visit 3.
- Shift in bilirubin from baseline to visit 3: A total of 222 (6.0%) betrixaban-treated patients and 222 (6.0%) enoxaparin-treated patients shifted from normal at baseline to high at visit 3.
- Shift in albumin values from baseline to visit 3: A total of 119 (3.2%) betrixaban-treated patients and 109 (2.9%) enoxaparin-treated patients shifted from normal at baseline to low at visit 3.

Reviewer comments: The shifts in laboratory values were similar between the treatments arms except for markers of anemia (hemoglobin, hematocrit) which were more common among patients treated with betrixaban. The shift in hemoglobin from normal to low was reported in 6.1% of patients in the betrixaban arm compared to 4.7% of patients in the enoxaparin arm.

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7.4.3 Vital Signs

The changes from baseline by visit in vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, and temperature) for the overall Safety population were submitted and reviewed. The two treatment groups were balanced at baseline with regard to vital signs. The changes in vital signs were comparable among the treatment groups.

Reviewer comments: Review of the vital signs changes during the treatment suggested that the changes were small and similar between the betrixaban and enoxaparin group.

7.4.4 Electrocardiograms (ECGs)

During the APEX trial ECGs were measured at baseline and visit 2 and read locally. In the overall safety population, the baseline ECG findings were: 1) interpreted as normal in 994 (27%) patients in the betrixaban group and 954 (26%) patients in the enoxaparin group, 2) interpreted as abnormal (clinically significant) in 363 (10%) patients in the betrixaban group and 350 (9%) patients in the enoxaparin group, 3) interpreted as abnormal (not clinically significant) 2322 (63%) in the betrixaban group and 2372 (64%) in the enoxaparin group.

At visit 2, the ECG findings were: 1) interpreted as normal in 1003 (27%) patients in the betrixaban group and 1000 (27%) patients in the enoxaparin group, 2) interpreted as abnormal (clinically significant) in 265 (7%) patients in the betrixaban group and 250 (7%) patients in the enoxaparin group, 3) interpreted as abnormal (not clinically significant) 2178 (59%) in the betrixaban group and 2187 (59%) in the enoxaparin group.

In the overall safety population no significant changes from baseline were seen in either treatment group for any of the ECG interpretation.

For more details refer to clinical pharmacology review.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were done.

7.4.6 Immunogenicity

NA

7.5 Other Safety Explorations

Reference ID: 4076151

7.5.1 Dose Dependency for Adverse Events

In the APEX study the incidence of adverse events in patients who received a reduced dose of betrixaban (40 mg) due to concomitant use of strong P-gp inhibitors was higher than those who received 80 mg of betrixaban (56% vs 52%, respectively). In addition, the rate of adverse events was higher in patients who received a dose reduction of betrixaban (40 mg) due to severe renal insufficiency (CrCl <30 mL/min) compared to those who received higher dose of betrixaban (80 mg) and did not have severe renal insufficiency (62% vs 52%, respectively).

The incidence of major/CRNM bleeding reported in the overall safety population in patients who received a lower dose of betrixaban (40 mg) was 4.8% compared to 2.7% in patients who received a higher dose of betrixaban (80 mg). A major bleeding rate of 1.4% was reported in patients who received lower dose of betrixaban (40 mg) compared to a rate of 0.5% in patients who received a higher dose of betrixaban (80 mg).

7.5.2 Time Dependency for Adverse Events

The incidence of major/CRNM bleeding reported in the overall safety population through the time of parenteral study medication discontinuation was 1.13% in the betrixaban group vs 0.73% in the enoxaparin group in the APEX trial. However, the incidence of major/CRNM bleeding reported in the overall safety population from the time of parenteral study medication discontinuation through 7 days after discontinuation of all study medication was 2.05% in the betrixaban group vs 0.89% in the placebo group in the APEX trial.

7.5.3 Drug-Demographic Interactions

The incidence of major bleeding was higher in female patients compared to male patients in the betrixaban arm (0.35% in male vs 0.94% in female). In patients who received the 80 mg dose of betrixaban the rate of major bleeding in women was 0.67% compared to 0.48% in the enoxaparin group and the event rate in men was 0.3% compared to 0.6% in the enoxaparin group. In patients who received the 40 mg dose of betrixaban the rate of major bleeding in women was 8/391 (2.05%) compared to 0/366 (0.00%) in the enoxaparin group and the event rate in men was 2/339 (0.59%) compared to 5/359 (1.39%) in the enoxaparin group.

The incidences of major or CRNM bleeding events in the betrixaban were similar in men (3.19%) and women (3.06%). The incidence of major or CRNM bleeding was higher in patients age ≥ 75 years compared to patients age < 65 years in the betrixaban arm (3.5% in ≥ 75 years vs 2.2% in < 75 years). The incidence of major or CRNM was less in patients age <65 years compared to patients age 65 years or older in the betrixaban arm (1.1% in <65 years vs 3.4% in ≥ 65 years). The incidence of major or CRNM bleeding in betrixaban arm was higher among patients in North America region 15/282 (5.3%) compared to non-North America region 101/3434 (2.9%). The rate of major or CRNM bleeding in the betrixaban arm was highest among patients in North America (5.3%) followed by Western Europe 38/771 (4.9%), with the least in Eastern Europe 59/2434 (2.4%).

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The percentage of patients with at least one TEAE or with an SAE between men and women were comparable between two treatment groups within each sex. The percentage of patients with at least one TEAE in betrixaban arm was similar between male (54%) and female (54%). The percentage of patients with at least one SAE in betrixaban arm was higher in male (20%) than in female (16%) patients.

Reviewer comment: In the APEX trial, the drug-demographic interaction showed that similar incidence of major or CRNM bleeding in male and female patients (3.2% vs 3.1%, respectively). However, the incidence of major bleeding was higher in female than male patients treated with betrixaban (0.94% and 0.34%, respectively). There was slightly higher incidence of SAEs among male patients than female patients treated with betrixaban (20%, 16%, respectively).

7.5.4 Drug-Disease Interactions

The subgroup analyses on patients with mild (CrCL ≥ 60 to < 90 mL/min), moderate (CrCL ≥ 30 to < 60 mL/min) or severe (CrCL < 30 mL/min) renal impairment (RI) at randomization, suggest that an increased rate of major bleeding with decreasing creatinine clearance in the betrixaban group (6/1287 [0.39%], 17/1582 [1.07%], 3/174 [1.72%] in mild, moderate and severe renal insufficiency, respectively). The rate of major bleeding in patients with severe renal insufficiency was higher in the betrixaban group 3/174 (1.72%) than that in the enoxaparin group 1/149 (0.67%).

In addition, there was a similar trend of an increased rate of major or CRNM bleeds with decreasing creatinine clearance in the betrixaban group (33/1287 [2.56%], 60/1582 [3.79], 9/174 [5.17] in mild, moderate and severe renal insufficiency, respectively). There was a higher rate of major/CRNM bleeding in patients with betrixaban with severe renal insufficiency 9/174 (5.17%) compared to enoxaparin 3/149 (2.01%).

There was a trend towards an increase in frequency of adverse events with decreasing renal function in both betrixaban and enoxaparin groups. In patients with mild, moderate, and severe renal impairment, respectively, the percentages of patients with at least one TEAE were 51.9%, 56.3%, 61.5% in the betrixaban group and 50.3, 50.1, and 58.4% in the enoxaparin group.

Reviewer comment: In the APEX trial, there was a trend of increased incidences of bleeding and AEs associated with decreasing creatinine clearance in patients with renal impairment treated with betrixaban.

7.5.5 Drug-Drug Interactions

In APEX trial concomitant use of aspirin was strongly discouraged. If aspirin was required for cardiovascular disease, doses were limited to < 165 mg QD, with the exception of patients who were receiving aspirin for an ischemic stroke or TIA indication, who could take 325 mg QD.

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The concomitant use of aspirin and betrixaban in patients resulted in a slightly increased incidence of major/CRNM bleeding compared to those who did not use aspirin (32/864 [3.7%] vs 50/1730 [2.89%], respectively). The rate of major/CRNM bleeding in patients who received aspirin and betrixaban was 34/1122 (3.01%) of patients. However, the concomitant use of aspirin with betrixaban resulted in an increased incidence of major bleeding twice as much as those who did not use aspirin with betrixaban (9/864 [0.93%] vs 8/1730 [0.46%], respectively).

In addition, in the betrixaban group, there was a greater number of patients who experienced stroke event among those patients who received concomitant aspirin 8/864 (0.93%) than among those who did not receive concomitant aspirin 5/1730 (0.29%).

Reviewer comments: In the APEX trial, there were trends of increased incidences of bleeding and stroke associated with concomitant use of aspirin with betrixaban. However, numbers of patients with events were small.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Refer to Pharmacology/Toxicology review.

7.6.2 Human Reproduction and Pregnancy Data

Pregnant or lactating women were excluded from the APEX study. The Applicant did not report any case of pregnancy while receiving betrixaban. It is not known if betrixaban is excreted in the human milk.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Applicant submitted an initial Pediatric Study Plan (PSP) to DHP on May 02, 2016. On September 27, 2016, DHP issued a letter to the sponsor confirming DHP agreement to the submitted Agreed-Upon Initial PSP.

The proposed pediatric studies include the following:

(b) (4)

2. (b) (4)

3. 

Reviewer comments: The proposed pediatric study plan appears to be adequate.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no patients in the course of betrixaban development program who took higher than prescribed dose. Single doses up to 550 mg and multiple doses up to 120 mg were not associated with clinically relevant adverse events.

Based on the mechanism of action of betrixaban and known class effects, an overdose may result in a hemorrhage. No antidote for betrixaban is currently available.

There is no indication that betrixaban has the potential for drug abuse.

7.7 Additional Submissions / Safety Issues

The betrixaban clinical development program included 20 Phase 1 clinical pharmacology studies, three phase 2 studies (one uncontrolled and two controlled) and one large phase 3 trial (APEX). The main source of the safety data came from the phase 3 pivotal study (APEX) in which a total of 3716 patients received betrixaban. Supportive safety data included three phase 2 completed clinical trials conducted to evaluate evaluated safety, tolerability and efficacy of betrixaban in other indications. The studies were conducted in patients with non-valvular atrial fibrillation (PN006, DEC and 08-015, EXPLORE Xa) and in surgical patients after unilateral total knee replacement (Study 05-003, EXPERT) and included a total 741 patients of who received betrixaban.

Phase 2 Clinical Trials (PN006, EXPLORE Xa, EXPERT)

PN006 (DEC): 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)

Design: This was a multicenter, open label, uncontrolled study in patients with nonvalvular atrial fibrillation. The primary objective was to assess whether weight-based dosing provides equivalent $C_{12}h$ exposures between two weight groups (lower weight: < 80 kg, higher weight: ≥ 80 kg) and reduces betrixaban PK variability. The secondary objective included the collection of safety data on long-term follow-up up to 24 weeks.

Exposure: Patients weighing < 80 kg received daily betrixaban 60 mg, patients weighing ≥ 80 kg received daily betrixaban 90 mg, and patients on amiodarone at screening, regardless of weight, received daily betrixaban 30 mg.

08-015 (EXPLORE Xa): A Phase 2, Randomized, Parallel Group, Dose-Finding, Multicenter, 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 in Patients With Non-Valvular Atrial Fibrillation (EXPLORE Xa)

Design: This was a randomized, multicenter, dose-finding study of patients with documented non-valvular atrial fibrillation. A total of 508 patients were randomized to 1 of 4 treatment groups (1:1:1:1 ratio) a fixed dose of 40 mg, 60 mg, or 80 mg betrixaban or adjusted dose of warfarin to target INR of 2.0 to 3.0. The study was open-label for warfarin, while the 3 daily doses of betrixaban (40, 60, or 80 mg) were double-blinded. Patients could be enrolled regardless of renal function as long as they were not receiving dialysis. The 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.

Exposure: Randomized patients received either betrixaban daily at fixed dose of 40, 60, or 80 mg or warfarin at a dose adjusted to maintain the target INR of 2.0 to 3.0. Each patient was treated for a minimum of 3 months.

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

Design: This was an open label phase 2 study in which approximately 200 patients undergoing unilateral knee replacement were randomized 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 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 at doses of 15 mg and 40 mg PO BID in the above subjects. Secondary objectives included to assess the PK and PD of betrixaban at doses of 15 mg and 40 mg PO BID.

Drug Exposure: Betrixaban was administered 6 to 8 hours after surgery and approximately every 12 hours thereafter; enoxaparin was administered 12 to 24 hours after surgery and twice daily

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thereafter. Drug administration continued until unilateral venography was performed on Day 10 to 14.

In the three phase 2 clinical trials, a total of 741 patients were exposed to orally administered betrixaban for at least one dose of 5 to 90 mg and up to 11 months duration.

Safety Results

Death: Three patients died in the phase 2 trials. No deaths were reported in Studies 05-003 (EXPERT) and PN006 (DEC). In Study 08-015 (EXPLORE Xa) there were 3 deaths, one in the 40 mg betrixaban group (cardiovascular, pump failure), one in the warfarin group (cardiovascular, sudden/arrhythmic) and one death due to respiratory failure occurred in the 80 mg betrixaban group within 30 days after the end of the study. All three deaths were considered unrelated to study drug.

Serious Adverse Events: In the DEC study, SAEs were reported in 13.2% of patients. In the EXPERT study, SAEs were reported in 7.1% of patients in the 40 mg betrixaban group and 3.4% of patients in 15 mg betrixaban group compared to 2.3% in enoxaparin group. In the EXPLORE Xa study, SAEs were reported in 9.2% of patients in the overall betrixaban group compared to 9.4% in the warfarin group.

Bleeding Events:

In the DEC study, there were 7 bleeding AEs including one major bleeding event (gastrointestinal hemorrhage).

In the EXPERT study, there were no major bleeding events and two clinically significant non-major bleedings were reported in the betrixaban 40 mg group (2.4%) compared to one subject with a major bleeding (2.3%) and 2 subjects with clinically significant non-major bleeds (4.7%) in the enoxaparin group.

In the EXPLORE Xa study, the warfarin-treated and in the 60 and 80 mg betrixaban-treated patients experienced an overall similar rate of bleeding events (5.5%, 3.9% and 3.9%, respectively). Major bleeds occurred only in patients taking betrixaban 80 mg or warfarin. At 90 days, both the betrixaban 80 mg dose group and the warfarin group had 3 patients with major bleeds. Between 90 and 150 days, two additional warfarin-treated patients and no additional betrixaban-treated patients experienced major bleeds.

120-Day Safety Update:

The applicant submitted the 120-day safety update on February 24, 2017. The submission contained the update of the original Summary of Clinical Safety (NDA 208383 Section 2. 7.4 (data cutoff date 11 March 2016) and covers the period March 11, 2016 through February 13, 2017. The applicant stated that during that period only one clinical study was ongoing:: (b) (4)

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Safety Summary

The review of safety for the proposed indication for prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for acute medical illness who had restricted mobility and other risk factors for VTE was primarily based on the safety results from APEX Study. The safety findings are as follows.

Bleeding:
The primary safety endpoint was the occurrence of major bleeding through seven days after discontinuation of all study drugs. The secondary safety outcomes included major or CRNM bleeding. The results suggested the following:

1. The rate of major bleeding which was reported in 25/3,716 (0.67%) patients in the betrixaban group and 21/3,716 (0.57%) patients in the enoxaparin group.
    a. The rate of major bleeding in betrixaban group was 15/2986 (0.5%) in patients who received 80 mg dose and 10/730 (1.4%) in patients who received a reduced dose of 40 mg. In patients who received dose reduction (40 mg of betrixaban) there was a numerical difference in number of patients who experienced major bleeding (10 cases in the betrixaban group vs 5 cases in the enoxaparin group).
    b. There were numerical imbalances in number of patients who experienced major gastrointestinal bleeding. Twice as many patients experienced major GI hemorrhage in the betrixaban arm (20 cases) than those in the enoxaparin arm (10 cases).
    c. There were numerical imbalances in number of patients who experienced major intracranial hemorrhages which was lower in the betrixaban group (2 cases) than in the enoxaparin group (7 cases).
    d. There was a significant increase in major bleeding in women treated with betrixaban (0.94%) compared to those treated with enoxaparin (0.40%).
    e. The rate of major bleeding in patients treated with betrixaban increased with decreased creatinine clearance.
2. The event rate of major or CRNM bleeds was higher in the betrixaban group (3.12%) than in the enoxaparin group (1.59%).
    a. Most common CRNM bleeding was GI bleed followed by hematuria.
    b. Approximately 60% of the CRNM bleeding events in the betrixaban did not required medical intervention.
    c. The rate of serious CRNM bleed was higher among patients in the betrixaban group compared enoxaparin group (1.2% vs 0.5%, respectively).
    d. Discontinuation of study drugs rate was higher in the betrixaban group than the enoxaparin group (1.5% vs 0.6%, respectively).
    e. The median duration of CRNM bleed was longer in the betrixaban group (3 days) than that in the enoxaparin group (2 days).

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   f. The event rate of major or CRNM bleeding appeared to increase with decreasing creatinine clearance and concomitant use of P-gp strong inhibitors in patients treated with betrixaban.

3. Although there were numerical elevations in hepatic transaminases seen in the betrixaban group, however, no hepatic Hy's rule cases were observed in the betrixaban treated patients. The incidence of liver enzyme elevations in the betrixaban group was comparable to the enoxaparin group.
4. The rate of treatment emergent adverse events (TEAEs) resulting in death was similar between the two treatment groups at approximately 6%.
5. The percentages of patients reporting at least one serious adverse event (SAE) in the two groups were comparable (18% for betrixaban vs. 17% for enoxaparin).
6. The percentages of patients reporting at least one nonfatal SAE in the two groups were comparable (14.3% for betrixaban vs. 12.9% for enoxaparin). However, the rate of nonfatal serious hemorrhagic events reported in the betrixaban group was double the rate of that reported in the enoxaparin group (2.4% vs 1.2%).
7. The overall incidence of TEAEs in the overall safety population in the betrixaban group (54%) was similar to that in the enoxaparin group (52%). The most common TEAEs in the overall safety population in both treatment groups were cardiac failure (4.7% in the betrixaban and 4.1% in the enoxaparin) and hypertension (3.7% in the betrixaban and 3.0% in the enoxaparin). Gastrointestinal disorder was the system organ class (SOC) with the highest incidence of treatment emergent adverse events (TEAEs) for the overall betrixaban group (12.5% in the betrixaban group vs. 10.8% in the enoxaparin group).

8 Postmarket Experience

There are no post-marketing data for betrixaban at the time of this application.

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9 Appendices

9.1 Literature Review/References

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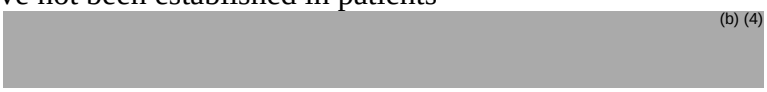
7. Alotaibi GS, Almodaimegh H, McMurtry MS, Wu C. Do women bleed more than men when prescribed novel oral anticoagulants for venous thromboembolism? A sex-based meta analysis. Thromb Res. 0049; 2013 Jul 26:doi 10.

9.2 Labeling Recommendations

The following were recommended in the betrixaban label.

- Betrixaban should be indicated for “prophylaxis of venous thromboembolism in adult patients hospitalized for an acute medical illness who have restricted mobility and other risk factors for VTE.”
- The recommended duration of treatment is 35 to 42 days.
- A limitation of betrixaban use should state that “the safety and efficacy of betrixaban have not been established in patients
  
  (b) (4)
  - with prosthetic heart valves.”
- In Section 6.1 Clinical Trials Experience,

  - Add detail description of the safety population
  - Add analysis results of the primary and secondary safety endpoints and the incidence of bleeding by anatomical site (adverse reaction related to bleeding)
  - Added a table summarizing the incidence of bleeding events (major or/and CRNM) by dose.
  - Add statement of significant bleeding identified in subgroup analyses.
  - Add a table summarizing common adverse reactions occurred in ≥ 1% of patients.
- In Section 14 Clinical Studies,
  - Add a table summarizing analysis results of the primary efficacy outcome and its components.
  - Add descriptive analysis results of the primary efficacy outcome in Cohort 1 and Cohort 2.
  - Add a table summarizing analysis results of the primary efficacy outcome and its components for patients who were randomized to take 80 mg betrixaban.
  - Add descriptive analysis results of the primary efficacy outcome for patients who were randomized to receive 40 mg betrixaban.
  - Delete (b) (4).
  - Delete (b) (4).
  - Delete (b) (4)
  - Add description of randomization stratification factors to the design of APEX Study.

9.3 Advisory Committee Meeting

No advisory committee was convened to review this application.

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/s/

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