NCT03310021

Protocol Amendment 5

A Phase 2 Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics/Pharmacodynamics of Andexanet Alfa Administered to Healthy Japanese and Caucasian Subjects

Document Date: 19-February-2019

A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY, AND PHARMACOKINETICS/PHARMACODYNAMICS OF ANDEXANET ALFA ADMINISTERED TO HEALTHY JAPANESE AND CAUCASIAN SUBJECTS

Drug Name:	andexanet alfa (PRT064445)
Protocol Number:	16-508
Phase:	2
IND	015089

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Amendment 5	19-February-2019
Amendment 4	01-February-2019
Amendment 3	16-November-2018
Amendment 2	04-December-2017
Amendment 1	08-September-2017
Original Protocol:	30-June-2017

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY, AND PHARMACOKINETICS/PHARMACODYNAMICS OF ANDEXANET ALFA ADMINISTERED TO HEALTHY JAPANESE AND CAUCASIAN SUBJECTS," and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312 and all locally applicable laws.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Portola Pharmaceuticals, Inc.

Signature of Principal Investigator

Dana Yee, MD
Name of Principal Investigator (Print)

20 FEB 2019
Date (DD Month YYYY)

SPONSOR'S AGREEMENT

I have read the attached protocol entitled "A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY, AND PHARMACOKINETICS/PHARMACODYNAMICS OF ANDEXANET ALFA ADMINISTERED TO HEALTHY JAPANESE AND CAUCASIAN SUBJECTS," and agree to abide by all provisions set forth therein.

I agree to comply with the ICH Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312 and all locally applicable laws.

Patrick Yue, MD
Senior Director
Clinical Development
Portola Pharmaceuticals, Inc.

19 feb 2019
Date (DD Month YYYY)

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LIST OF ABBREVIATIONS

Term	Definition
ACT	Activated clotting time
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BID	Twice daily
BP	Blood pressure
b-TG	Beta thromboglobulin
CFR	Code of Federal Regulations
CL	Clearance
CLr	Renal clearance
$C_{max/min}$	Maximum/minimum observed concentration
CRF	Case report form
CRO	Contract research organization
DVT	Deep venous thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
e-CRF	Electronic case report form
F1+2	Prothrombin fragment 1+2
FDA	(US) Food and Drug Administration
FSH	Follicle-stimulating hormone
FX	Factor X
FXa	Factor Xa
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HR	Heart rate
HRT	Hormone replacement therapy
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ICF	Informed Consent Form
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board

Term	Definition
ISC	Independent Safety Committee
IV	Intravenous
LCMS	Liquid chromatography mass spectrometry
λz	Terminal or elimination rate constant
MI	Myocardial infarction
min	Minute
mL	Milliliter
ng	Nanogram
PAP	Plasmin-antiplasmin complex
PD	Pharmacodynamic
PE	Pulmonary embolism
PF4	Platelet Factor 4
PK	Pharmacokinetic
PO	Orally
PT	Prothrombin time
Q	Every
QD	Once daily
RAST	Radioallergosorbent
RR	Respiratory rate
RVVT	Russell's Viper Venom Time
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
sTM	Soluble thrombomodulin
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Half-life
TAFI	Thrombin activatable fibrinolysis inhibitor
TAT	Thrombin-antithrombin complex
TEAE	treatment-emergent adverse event
TFPI	Tissue factor pathway inhibitor
T_{max}	Time to maximum observed concentration
tPA	Tissue plasminogen activator
ULN	Upper limit of normal
V_{ss}	Volume at steady state
VTE	Venous thromboembolism

PROTOCOL SYNOPSIS

Title	A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics/Pharmacodynamics of Andexanet Alfa Administered to Healthy Japanese and Caucasian Subjects
Study Number	16-508
Study Phase	2
Target Patient Population	Healthy Japanese subjects dosed to steady state with apixaban, rivaroxaban, and edoxaban; healthy Caucasian subjects dosed to steady state with apixaban
Objectives	The objectives of this study are to assess the following in healthy subjects dosed to steady state with direct oral FXa inhibitors (apixaban, rivaroxaban, and edoxaban): Primary Efficacy Objective • To compare andexanet and placebo with respect to reversal of each FXa inhibitor as measured by anti-fXa activity. Secondary Efficacy Objectives • To assess andexanet and placebo with respect to reversal of each FXa inhibitor as measured by free fraction of the inhibitor. • To assess andexanet and placebo with respect to reversal of each FXa inhibitor as measured by restoration of thrombin generation. • To assess the pharmacodynamics of andexanet in Japanese subjects and Caucasian subjects, as measured by anti-fXa activity, free fraction of the FXa inhibitor (apixaban), and restoration of thrombin generation. Safety Objective • To evaluate the safety of andexanet in Japanese subjects. Pharmacokinetics Objectives • To evaluate the pharmacokinetics of andexanet in Japanese subjects. • To compare the pharmacokinetics of andexanet in Japanese subjects to the pharmacokinetics of andexanet in Caucasian subjects.
Study Design	This is a single-center, randomized, double-blind, and placebo-controlled trial designed to: 1) demonstrate the degree to which administered andexanet doses can reverse FXa-inhibitor-induced anticoagulation; and 2) evaluate the safety and PK of andexanet in healthy Japanese subjects taking direct FXa inhibitors at therapeutic doses. Reversal of anticoagulation will be evaluated by measuring anti-fXa activity, unbound FXa inhibitor plasma levels, and thrombin generation. The study is divided into two parts, Part 1 is to evaluate andexanet reversal effect in the Japanese subjects, safety, and PK/PD, and also evaluate similarity with Caucasian data when andexanet is administered 4 hours after FXa inhibitor dosing. Part 2 will be conducted to evaluate andexanet reversal effect of FXa inhibitor dosing regimens and the administration of andexanet at 8 hours after FXa inhibitor dosing. The design of Part 2 may be adjusted based on Part 1 outcomes. Following screening, study subjects will be randomized and domiciled at the study site for ~10 days, during which time they will be administered apixaban, rivaroxaban, or edoxaban (depending on cohort; see table) on Days 1–6. Andexanet (or matching placebo) bolus and continuous infusion doses will be administered on Day 6, at various times after the last administration of FXa inhibitor. Study subjects will be discharged from the clinical site on Day 10 and followed for safety through Day 36 (+3). The primary endpoint is the difference in the percent change from baseline anti-fXa activity between andexanet- and placebo-treated subjects in each cohort. That is, the percent change from baseline (where baseline is the time point immediately prior to the administration of

Study Design (Cont'd)

andexanet) in anti-fXa activity to its nadir as measured during the evaluation period. Nadir is defined as the smallest value for anti-fXa activity between the 110-minute time point (10 minutes prior to the end of the continuous andexanet infusion) and the 5-minute time point after the end of the continuous infusion (inclusive).

The study will be conducted in up to 10 cohorts grouped into two parts. Part 1 (with 5 cohorts) will enroll first. Based on the results of Part 1, Part 2 will be carried out (with up to 5 additional cohorts). To compare the PK of andexanet between Japanese and Caucasian subjects, Cohort 5 will include Caucasian subjects administered 5 mg BID apixaban followed by the stipulated andexanet dose (400 mg bolus followed by 4 mg/min infusion for 2 hours). For all cohorts, placebo groups are included for assessment of the efficacy and safety of andexanet in healthy volunteers.

For all cohorts, subjects will be randomized in a 2:1 ratio of treatment with andexanet or placebo, respectively. If enrolled subjects discontinue early from the study or have missing data for any reason, the Sponsor may elect to add up to 3 additional subjects (with newly blinded treatment assignments) within the discontinued subject's assigned cohort.

Part 1 will include the following cohorts:

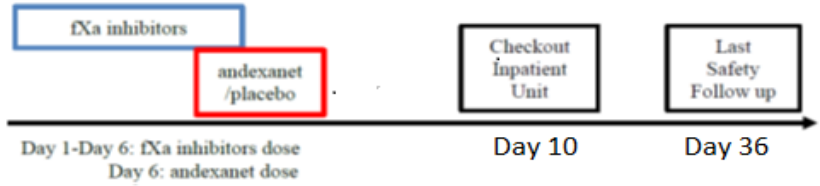
Cohort	FXa Inhibitor	Andexanet	N (Active/Placebo)
1	Apixaban 5 mg BID	400 mg bolus + 4 mg/min 120 minute infusion/placebo (andexanet dosing at 3 hours post-apixaban)	Japanese 9 (6/3)
2	Rivaroxaban 15 mg BID	800 mg bolus + 8 mg/min 120 minute infusion/placebo (andexanet dosing at 4 hours post-rivaroxaban)	Japanese 9 (6/3)
3	Edoxaban 60 mg QD	800 mg bolus + 8 mg/min 120 minute infusion/placebo (andexanet dosing at 3 hours post-edoxaban)	Japanese 12 (8/4)
4	Edoxaban 60 mg QD	800 mg bolus + 8 mg/min 120 minute infusion/placebo (andexanet dosing at 90 minutes post-edoxaban)	Japanese 12 (8/4)
5	Apixaban 5 mg BID	400 mg bolus + 4 mg/min 120 minute infusion/placebo (andexanet dosing at 3 hours post-apixaban)	Caucasian 9 (6/3)

Study Design (Cont'd)

Part 2 will include the following cohorts:

Cohort	FXa Inhibitor	Andexanet	N (Active/Placebo)
6	Apixaban 10 mg BID	800 mg bolus + 8 mg/min 120 minute infusion/Placebo (andexanet dosing at 3 hours post apixaban)	Japanese 9 (6/3)
7	Edoxaban 30 mg QD	400 mg bolus + 4 mg/min 120 minute infusion/placebo (andexanet dosing at 90 min post edoxaban)	Japanese 12 (8/4)
8	Apixaban 10 mg BID	400 mg bolus + 4 mg/min 120 minute infusion/placebo (andexanet dosing at 8 hours post apixaban)	Japanese 9 (6/3)
9	Rivaroxaban 15 mg BID	400 mg bolus + 4 mg/min 120 minute infusion/placebo (andexanet dosing at 8 hours post rivaroxaban)	Japanese 15(10/5)
10	Edoxaban 60 mg QD	400 mg bolus + 4 mg/min 120 minute infusion/placebo (andexanet dosing at 8 hours post edoxaban)	Japanese 12 (8/4)

Study Schematic



Study Periods

- Screening: Days -45 days to -1 day
- Anticoagulant Dosing: Days 1 to 6 (only morning dose on Day 6 for apixaban, rivaroxaban, and edoxaban)
- Andexanet Dosing: Day 6
- Safety Follow-up: Days 7 to 36 (+3)

Inclusion Criteria	To be eligible for study enrollment, study subjects must meet the following inclusion criteria: 1) Must be in reasonably good health as determined by the Investigator based on medical history, full physical examination (including blood pressure and pulse rate measurement), 12-lead ECG, and clinical laboratory tests. Subjects with well-controlled, chronic, stable conditions (e.g., controlled hypertension, non-insulin dependent diabetes, osteoarthritis, hypothyroidism) may be enrolled based on the clinical judgment of the Investigator. 2) For all cohorts except Cohort 5, subjects must be of Japanese ethnicity, defined as having four ethnic Japanese grandparents. Subjects may not have lived outside of Japan for more than 10 years. For Cohort 5, subjects must be of Caucasian race. 3) Must be between the ages of 18 and 75 years, inclusive, at the time of signing of the ICF. 4) Agrees to have any dietary or nutritional supplements reviewed by the Investigator and potentially held during the study if advised by the Investigator. Standard multivitamin and mineral supplementation will be permitted. 5) Agrees to comply with the contraception and reproduction restrictions of the study: • Men whose sexual partner is of childbearing potential and/or who are not monogamous must be using two acceptable methods of contraception, at least one of which must be a barrier method (e.g., spermicidal gel plus condom), for the entire duration of the study and for at least 1 month following study-drug administration; and men must refrain from attempting to father a child or donating sperm in the 1 month following the study-drug administration. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. • Men who report surgical sterilization (e.g., bilateral vasectomy) must have had the procedure at least 6 months before study drug administration. • Surgical sterilization procedures should be supported with clinical documentation and noted in the Relevant Medical History/Current Medical Conditions section of the CRFs. • Women of childbearing potential must be using two medically acceptable methods of contraception, at least one of which must be a barrier method (e.g., non-hormone containing intra-uterine device plus condom, spermicidal gel plus condom, diaphragm plus condom), from the time of Screening and for the duration of the study, through at least 1 month following study drug administration. NOTE: Oral and topical hormonal contraceptive use, as well as the use of hormone-containing intra-uterine devices, is not permitted due to their increased risk of thromboembolism. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post- ovulation methods) and withdrawal are not acceptable methods of contraception; OR • Postmenopausal women must have had no regular menstrual bleeding for at least 1 year before initial dosing and either be over the age of 60 years or have an elevated plasma follicle-stimulating hormone (FSH) level (i.e., > 40 mIU/mL) at Screening OR • Women who report surgical sterilization (i.e., hysterectomy, tubal ligation, and/or bilateral oophorectomy) must have had the procedure at least 6 months before study drug administration. Surgical sterilization procedures should be supported with clinical documentation and noted in the Relevant Medical History/Current Medical Conditions section of the CRF; AND • All female subjects must have a documented negative pregnancy test result at Screening and on Study Day -1.

Inclusion Criteria (Cont'd)	6) Systolic blood pressure < 160 mmHg and diastolic blood pressure < 90 mmHg at Screening and Day -1. 7) The following laboratory values must be within the normal laboratory reference range within 45 days of Day -1: PT, aPTT, and ACT; hemoglobin, hematocrit, and platelet count. 8) The following laboratory values must be equal to or below 2 times the upper limit of normal (ULN) range within 45 days of Day -1: Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) and total bilirubin. 9) The Screening serum creatinine must be below 1.5 mg/dL within 45 days of Day -1. 10) Body mass index of less than 30 kg/m^2, inclusive, and body weight between 50 kg and 80 kg, inclusive, at Screening. In addition, subjects must be greater than 60 kg for Cohorts 3, 4, and 10. 11) Agrees to abstain from alcohol consumption for the duration of the domicile period, and from the use of drugs of abuse for the duration of the study. 12) Able to read and give written informed consent and has signed a consent form approved by the Investigator's Institutional Review Board (IRB) or Independent Ethics Committee (IEC).
Exclusion Criteria	To be eligible for study enrollment, potential study subjects must <u>not</u> meet the following exclusion criteria: 1) Previous use of andexanet or previous participation in the current study (even if the subject received placebo). 2) History of abnormal bleeding, signs or symptoms of active bleeding, or risk factors for bleeding. 3) Has a stool specimen that was positive for occult blood within 6 months of study Screening or during the Screening Period. 4) Past or current medical history of thrombosis, any sign or symptom that suggests an increased risk of a systemic thrombotic condition or thrombotic event, or recent events that may increase risk of thrombosis. a. For example, subjects with a known or suspected hypercoagulable state, history of VTE, DVT, stroke, myocardial infarction (MI), cancer (other than non-melanoma skin cancer), atrial fibrillation, heart failure, cardiomyopathy, phlebitis, lower extremity edema, major surgery, or trauma within 2 months of Study Day -1, airplane travel with a planned flight time for any single flight segment ≥ 6 hours during the 4 weeks prior to Study Day -1, or general immobility are excluded. 5) Absolute or relative contraindication to anticoagulation or treatment with apixaban, rivaroxaban, and/or edoxaban. 6) Prior consumption of (by any route) one or more doses of aspirin (including baby aspirin), salicylate or subsalicylate, other antiplatelet drugs (e.g., ticlopidine, clopidogrel), non-steroidal anti-inflammatory drugs, fibrinolytic, or any anticoagulant within 7 days prior to Day -1 or is anticipated to require such drugs during the study. 7) Receipt of (by any route) hormonal contraception, post- menopausal hormone replacement therapy (HRT) (including over-the-counter products), or testosterone during the 4 weeks prior to Study Day -1 or is anticipated to require such drugs during the study. 8) Family history of or risk factors for a hypercoagulable or thrombotic condition, including one of the following: a. Factor V Leiden carrier or homozygote. b. Protein C, S, or ATIII activity below the normal range. 9) History of adult asthma or chronic obstructive pulmonary disease or current regular or as-needed use of inhaled medications. 10) Active HBV, HCV, or HIV-1/2 infection.

<table>
<tr><td></td><td>11) Use of any drugs that are strong dual inhibitors or inducers of CYP3A4 (apixaban and rivaroxaban cohorts only) and P-gp (all cohorts) within 7 days prior to Study Day -1 or anticipated need for such drugs during the study.
12) Participation in an investigational drug study within 45 days of Day -1 or Day -1 is within 5 half-lives of the investigational compound.
13) Positive screen for drugs of abuse at Day -1 that is not explained by a prescription medication that the subject is known to be taking.
14) A medical or surgical condition that may impair drug (anticoagulant or andexanet) metabolism.
15) Allergy to any of the vehicle ingredients: Tris, arginine, sucrose, hydrochloric acid, mannitol, and polysorbate 80.
16) Allergy to soy or soy products.
17) Current breastfeeding or a positive pregnancy test at Screening or Day -1.
18) Any condition that could interfere with, or for which the treatment might interfere with, the conduct of the study or interpretation of the study results, or that would in the opinion of the Investigator increase the risk of the subject's participation in the study. This would include but is not limited to alcoholism, drug dependency or abuse, psychiatric disease, epilepsy, or any unexplained blackouts.
19) The subject is not judged by the study staff to have adequate bilateral venous access.
20) Unwillingness to adhere to the activity requirements of the study.</td></tr>
<tr><td>Test Product, Dose, and Mode of Administration</td><td>The andexanet dose regimens to be examined in this study are as follows (see table below):
• Cohorts 1, 5, 7, 8, 9, and 10: 400 mg IV bolus at a target rate of approximately 30 mg/min, followed by a continuous infusion of 480 mg at 4 mg/min for 120 minutes.
• Cohorts 2, 3, 4, and 6: 800 mg IV bolus at a target rate of approximately 30 mg/min, followed by a continuous infusion of 960 mg at 8 mg/min for 120 minutes.
<table>
<tr><th>Cohort</th><th>Test Product</th><th>Dose /Mode of Administration</th></tr>
<tr><td>1, 5, 7, 8, 9, 10</td><td>andexanet 200 mg Vial</td><td>400 mg bolus + 4 mg/min
120 minutes infusion IV</td></tr>
<tr><td>2, 3, 4, 6</td><td>andexanet 200 mg Vial</td><td>800 mg bolus + 8 mg/min
120 minutes infusion IV</td></tr>
</table></td></tr>
<tr><td>Reference Therapy and Mode of Administration</td><td>Placebo 400 mg or 800 mg (depending on cohort) dosed via IV bolus at a target rate of approximately 30 mg/min, followed by a continuous infusion at 4 mg/min or 8 mg/min (depending on cohort) for 120 minutes.</td></tr>
</table>

Efficacy Endpoints	**Primary Efficacy Endpoint** The primary efficacy endpoint is the difference in percent change in the anti-fXa activity from baseline to the nadir, where nadir is defined as the smallest value for anti-fXa activity between the 110-minute time point (10 minutes prior to the end of the continuous infusion) and the 5- minute time point after the end of the continuous infusion (inclusive). The primary analysis will be performed on all individual cohorts separately. **Secondary Efficacy Endpoints** • The percent change from baseline in anti-fXa activity at its nadir, where nadir is defined as the smallest value for anti-fXa activity at the +2 minute or +5 minute time point after the completion of the andexanet bolus. • The change from baseline in free FXa inhibitors concentration (ng/mL) at its nadir, where nadir is defined as the smallest value for free FXa inhibitors at the +2 minute or +5 minute time point after the completion of the andexanet bolus. • The change from baseline in free FXa inhibitors concentration (ng/mL) at its nadir, where nadir is defined as the smallest value for free FXa inhibitors between the 110-minute time point (10 minutes prior to the end of the continuous infusion) and the 5-minute time point after the end of the continuous infusion (inclusive). • The change in thrombin generation from baseline to its peak, where peak is defined as the largest value for thrombin generation between the +2 minute time point and the +5 time point after the end of the andexanet bolus (inclusive). • The occurrence of thrombin generation above the lower limit of the normal range at its peak, between the +2 minute time point and the +5 time point after the end of the andexanet bolus (inclusive). • The change in thrombin generation from baseline to its peak, where peak is defined as the largest value for thrombin generation between the 110-minute time point (10 minutes prior to the end of the continuous infusion) and the 5-minute time point after the end of the continuous infusion (inclusive). • The occurrence of thrombin generation above the lower limit of the normal range at its peak, where peak is defined as the largest value for thrombin generation between the 110-minute time point (10 minutes prior to the end of the continuous infusion) and the 5-minute time point after the end of the continuous infusion (inclusive) and assess the thrombin generation during 24 hours after administration of FXa inhibitors. **Exploratory Efficacy Endpoints** • For Parts 1 and 2 of the study, tissue factor pathway inhibitor (TFPI) activity, a marker of endogenous anticoagulation, will be evaluated for the purpose of monitoring the potential procoagulant activity of andexanet (due to andexanet-TFPI interaction). • For Part 1 of the study the following markers will also be examined: PT, aPTT, ACT, FX, fibrinogen, tPA, PAP, TAFI, TFPI (total and free antigen), b-TG, PF4, and sTM.
Safety Endpoints	The following safety parameters will be analyzed: • Adverse events, physical exam, vital signs, oxygen saturation, ECG, clinical laboratory values Serial clinical assessments for venous thromboembolic events. • Antibodies to andexanet, FX, FXa, and HCPs; neutralizing antibodies to andexanet, FX, and FXa. • Coagulation markers: D-dimer, F1+2, and TAT. RVVT will be collected in Part 1 only.

Pharmacokinetic Endpoints	Andexanet: Blood samples for andexanet will be collected at multiple time points on Day 6 through Day 8. • The following non-compartmental PK parameters will be computed for plasma andexanet: C_{max}, T_{max}, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-}\infty)}$, $t_{1/2}$, CL, V_{ss}, and λz. • The following non-compartmental parameter estimates will be evaluated to compare the pharmacokinetics of andexanet in Japanese versus Caucasian subjects; C_{max}, $AUC_{(0\text{-}\infty)}$, $t_{1/2}$, CL, V_{ss}, and λz. Factor Xa inhibitors: Plasma concentrations of both unbound and total FXa inhibitors will be measured in this study. Blood samples for FXa inhibitors (total and unbound) will be collected on Day 1 (pre-dose only), multiple time points on Day 5 through Day 8 and once on Day 9 and Day 10. • The following non-compartmental PK parameters will be computed for total plasma apixaban, rivaroxaban, edoxaban, and the edoxaban metabolite D21-2393: C_{max}, C_{bolus} (end of bolus + 2 minutes), T_{max}, CL/F, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-}\tau)}$, $t_{1/2}$, and λz.
Statistical Methods Analysis	**Analysis populations:** The safety analysis population will include all enrolled subjects who received any amount of study drug (andexanet or placebo) treatment. The efficacy analysis population will include all randomized subjects who took any amount of study medication (andexanet or placebo) during the double-blind treatment period. For the efficacy analysis, subjects will be presented in the treatment group to which they were randomized. Subjects will be included in the efficacy analysis set on change or percent change from baseline if they have a baseline value and at least one measurement post-baseline for the time point under consideration. The PK analysis populations will consist of all subjects who receive study drug and have sufficient data to calculate each PK parameter. **Efficacy endpoint analyses:** The primary analysis will be performed to compare the difference in the primary endpoint between andexanet- and placebo-treated subjects by cohort. The analysis will be performed in all cohorts. The comparison will be conducted using a two sample exact Wilcoxon rank sum test. All hypothesis tests will be 2-sided and performed at the 0.05 significance level. No adjustment for multiplicity is necessary since each cohort is considered as an independent population. No formal statistical hypothesis testing will be performed for the secondary endpoints but point estimates and two-sided 95% confidence intervals will be produced to assess the treatment effects with respect to the secondary endpoints.
Sample Size Determination	**Part 1:** **Apixaban 5 mg BID (Cohort 1 and Cohort 5)** The mean (SD) of the primary endpoint in Study 14-503 Part 2 which assessed the reversal of apixaban 5 mg BID anticoagulation with andexanet administered as an IV bolus followed by a 2-hour infusion were -92.3% (SD = 2.8%) and -32.7% (SD = 5.6%) for andexanet and placebo arms, respectively. Based on these results, the percent changes from baseline in anti-fXa activity in this study are assumed to be -90% (SD = 5%) and -35% (SD = 10%) for andexanet and placebo arms, respectively. The standard deviations in both arms are assumed larger than the observed values in the previous study to provide adequate power for the comparison. Under these assumptions, a total number of 9 subjects (6 active and 3 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test.

Sample Size Determination (Cont'd)	**Rivaroxaban 15 mg BID (Cohort 2)** The mean (SD) of the primary endpoint in Study 14-504 Part 2 which assessed the reversal of rivaroxaban 20 mg QD anticoagulation with andexanet administered as an IV bolus followed by a 2-hour infusion were -96.7% (SD = 1.8%) and -44.8% (SD = 11.7%) for andexanet and placebo arms, respectively. Based on these results, the percent changes from baseline in anti-fXa activity are assumed to be -90% (SD = 5%) and -45% (SD = 15%) for andexanet and placebo arms, respectively. Under these assumptions, a total number of 9 subjects (6 active and 3 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test. **Edoxaban 60 mg QD (Cohort 3: andexanet dosing at 3 hours post-edoxaban)** In Cohort 2 of Study 12-502 Module 4 which assessed the reversal of edoxaban anticoagulation with andexanet, the mean (SD) of the percent change from baseline anti-fXa activity at the end of infusion was -70.28% (SD = 5.64%) for the andexanet arm. In Cohort 1 and Cohort 2 of the same study, the mean (SD) of the percent change from baseline at 2 hours after the end of bolus was -40.31% (SD = 12.25%) for placebo. Based on these results, the percent changes from baseline in anti-fXa activity for andexanet and placebo are assumed as -70% (SD = 6%) and -40% (SD = 15%), respectively. Under these assumptions, a total number of 12 subjects (8 active and 4 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test. **Edoxaban 60 mg QD (Cohort 4: andexanet dosing at 90 minutes post-edoxaban)** There are no actual data of andexanet administration at 90 minutes after edoxaban dosing. Based on the result predicted by the PK-PD model developed using the data of Study 12-502, the percent changes from baseline in anti-fXa activity for andexanet and placebo are assumed as -70% (SD = 15%) and -30% (SD = 15%), respectively. Under these assumptions, a total number of 12 subjects (8 active and 4 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test. **Part 2:** **Apixaban 10 mg BID (Cohort 6: andexanet dosing at 3 hours post apixaban)** A total number of 9 subjects (6 active and 3 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test. The underlying assumptions are supported by data from Cohort 8 of the 16-512 study, which the mean (SD) of %change from baseline in anti-fXa activity (%CHB in anti-fXa activity) at nadir around EOI were -97% (SD = 0.8%) and –36% (SD = 3.3%) for andexanet and placebo arms, respectively. In the power calculation, -95% (SD = 10%) and -40% (SD = 10%) are assumed. **Edoxaban 30 mg QD (Cohort 7: andexanet dosing at 90 min post edoxaban)** A total number of 12 subjects (8 active and 4 placebo) will provide approximately 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test. Given the dose proportionality, the underlying assumptions are supported by data from Cohort 4 of the 16-508 study, which the mean (SD) of %CHB in anti-fXa activity at nadir around EOI were -71% (SD = 13.6%) and –34% (SD = 12.8%) for andexanet and placebo arms, respectively. In the power calculation, -70% (SD = 15%) and -35% (SD = 15%) are assumed. **Apixaban 10 mg BID (Cohort 8: andexanet dosing at 8 hours post apixaban)** A total number of 9 subjects (6 active and 3 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test. For placebo arm, the underlying assumptions are supported by data from Cohort 8 of the 16-512 study, which the mean (SD) of %CHB in anti-fXa activity at 3.5 hours after EOI was -51% (SD = 9.5%). For andexanet arm, the mean of %CHB in anti-fXa activity predicted by the PK-PD model that is 91.6% was used as reference because there are no actual data. In the power calculation, -90% (SD = 10%) and -50% (SD = 10%) are assumed.

Sample Size Determination (Cont'd)	**<u>Rivaroxaban 15 mg BID (Cohort 9: andexanet dosing at 8 hours post rivaroxaban)</u>** A total number of 15 subjects (10 active and 5 placebo) will provide approximately 87% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test. For placebo arm, the underlying assumptions are supported by data from Cohort 2 of the 16-508 study, which the mean (SD) of %CHB in anti-fXa activity at 1.5 hours after EOI was -56% (SD = 12.1%). For andexanet arm, the mean of %CHB in anti-fXa activity predicted by the PK-PD model that is 86.5% was used as reference because there are no actual data. In the power calculation, -85% (SD = 15%) and -55% (SD = 15%) are assumed. **<u>Edoxaban 60 mg QD (Cohort 10: andexanet dosing at 8 hours post edoxaban)</u>** A total number of 12 subjects (8 active and 4 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test. The underlying assumptions are supported by data from Cohort 11 of the 16-512 study, which the mean (SD) of %CHB in anti-fXa activity at nadir around EOI were -64% (SD = 9.0%) and –39% (SD = 6.0%) for andexanet and placebo arms, respectively. In the power calculation, -65% (SD = 10%) and -40% (SD = 10%) are assumed.
Study Centers	One study site in the US.

1.0 INTRODUCTION

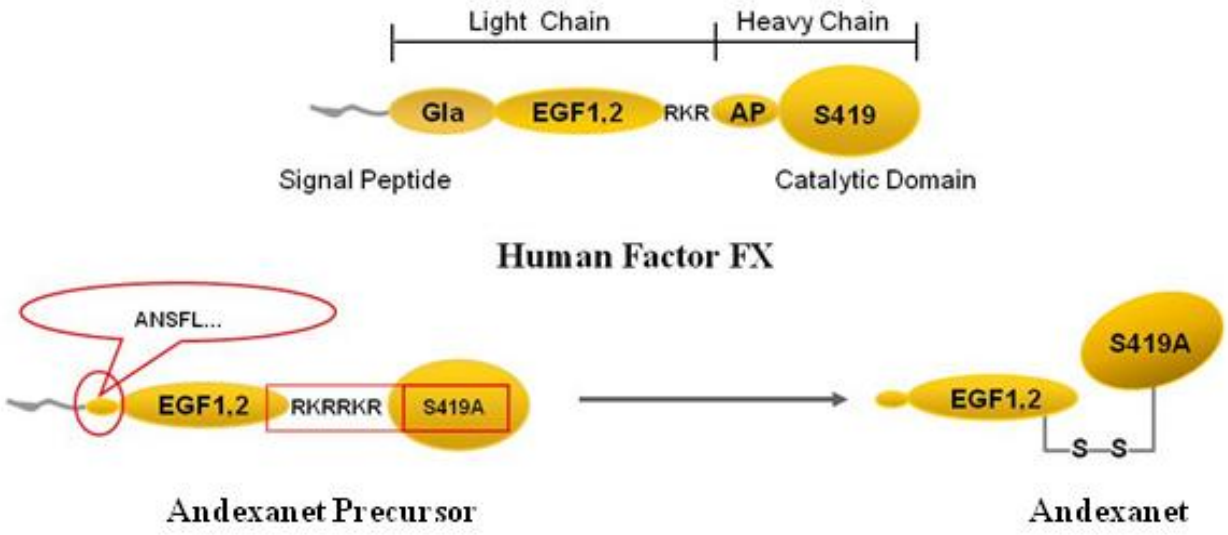
1.1. Background

Anticoagulant medications are frequently utilized for a variety of indications, including stroke prophylaxis in atrial fibrillation, the prevention of venous thromboembolism in hip or knee replacement surgery, and the prevention and treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE). In recent years a new class of oral anticoagulants, direct factor Xa (FXa) inhibitors, has been approved for use in the above indications (Appendix D to Appendix F). These drugs (including apixaban, edoxaban, and rivaroxaban) have become widely adopted after demonstrating a favorable safety and efficacy profile, as well as increased ease of use, versus vitamin K antagonists such as warfarin. Despite the popularity of these drugs, a significant limitation has been the lack of a reversal agent to be used in cases of severe and/or life-threatening bleeding events. There is thus currently an unmet medical need for an approved effective antidote for these drugs. With the increasing use of direct FXa inhibitors in contemporary clinical practice, this need is only expected to increase in the coming years.

1.2. Description of Andexanet

Andexanet alfa is a recombinant version of human FXa that has been rationally modified to render it functionally inactive (Figure 1). To achieve this aim, two key structural modifications were made to native human FXa. First, the substitution of a serine residue with an alanine at the active site eliminated the protein's catalytic activity. Second, the removal of the Gla domain eliminates its ability to assemble into the prothrombinase complex thus removing any anticoagulant effect. Reversal of anticoagulation is achieved because andexanet retains the ability to bind FXa inhibitor drugs with high affinity, thereby preventing them from binding to and inhibiting native FXa.

Figure 1: Structures of Human Factor X and Andexanet



Additional information about the mechanism and structure of andexanet can be found in the andexanet Investigator's Brochure.

1.3. Summary of Relevant Nonclinical Experience with Andexanet

1.3.1. Nonclinical Pharmacology

In vivo animal models have been used to demonstrate the correlation between reversal of the anticoagulant effects of direct FXa inhibitors (e.g., apixaban, edoxaban, rivaroxaban) and indirect FXa inhibitors (e.g., enoxaparin, fondaparinux) as measured by pharmacokinetic (PK) and pharmacodynamic (PD) parameters (such as plasma unbound fraction of the anticoagulant, whole blood international normalized ratio [INR], anti-fXa activity, and reduction of blood loss in anticoagulated rodents [1, 2] and rabbits [3, 4]).

In a more clinically relevant *in vivo* model of visceral bleeding caused by liver laceration refs[3-5], andexanet was administered to rivaroxaban-anticoagulated rabbits either prophylactically or following tissue injury. Intravenous bolus andexanet administration reversed rivaroxaban-induced anticoagulation as measured by plasma anti-fXa activity (97% decrease), prothrombin time (PT; 77% decrease), and unbound fraction of the anticoagulant (93% decrease); these PD markers correlated with reduction of blood loss (76% decrease) as compared to vehicle controls.

Taken together, the results from these two different pre-clinical bleeding models demonstrate a strong correlation between reversal of anti-fXa activity, decrease in free fraction of anticoagulant, and decrease in blood loss. These data support the hypothesis that andexanet rapidly binds and sequesters the FXa inhibitor, thus reversing the anticoagulant effect of FXa inhibition and allowing for the return of thrombin generation, which mediates restoration of normal hemostatic mechanisms.

Additional information about these experiments can be found in the andexanet Investigator's Brochure.

1.3.2. Nonclinical Toxicology and Safety

Good Laboratory Practice (GLP) toxicology studies have been conducted in both the rat and cynomolgus monkey. Andexanet was evaluated in two 14-day repeat dose toxicology studies, one each in the rat and monkey. Both toxicology studies performed administered andexanet twice daily (BID) as a maximal feasible dose (60 mg/kg/day), either daily for 14 days (rats) or every third day (cynomolgus monkeys), followed by a 28-day recovery period. There were no test article-related adverse effects in either study. In the more relevant species, cynomolgus monkeys, the animals were administered andexanet in the presence and absence of an FXa inhibitor (rivaroxaban, apixaban, betrixaban, or enoxaparin). The only significant finding in the 14-day repeat bolus IV study was a male monkey, dosed 60 mg/kg/day with andexanet that on Day 13 of the study (last dose) experienced anaphylaxis immediately after dosing. This animal recovered with administration of antihistamines and epinephrine. Based on the lack of adverse findings in both species at the highest doses tested, the No Observed Adverse Effect Level (NOAEL) dose in rat and cynomolgus monkeys is 60 mg/kg/day.

As might be expected after repeated dosing with a foreign protein in an animal species, all groups of monkeys and rats receiving andexanet developed antibodies to andexanet that persisted to the end of the 4-week recovery period. Despite the presence of these antibodies, andexanet was still able to reverse the anticoagulant effect of FXa inhibitors from Day 1 to Day 14 in cynomolgus monkey studies *in vitro* or *in vivo*. Antibody development in both rat and cynomolgus monkey studies did not change the toxicokinetics of andexanet from Day 1 to Day 14. Russell's Viper Venom Time (RVVT) was used to measure antibody production against endogenous FX or FXa and no changes suggestive of antibodies against FX or FXa were seen in RVVT measurements in monkeys administered andexanet.

There were no adverse findings in the male rat central nervous system and respiratory safety pharmacology studies up to, and including, the maximum feasible dose of 30 mg/kg when administered by IV bolus. Additionally, andexanet was evaluated for cardiovascular safety as a component study of the 14-day repeat IV bolus study in cynomolgus monkeys and was found not to affect electrocardiographic or blood pressure parameters.

Additional details from these studies can be found in the andexanet Investigator's Brochure.

1.4. Summary of Clinical Experience with Andexanet in Healthy Subjects

Andexanet has been studied in 211 healthy subjects in 5 completed studies. The trials include a completed single ascending dose Phase 1 study (Study 11-501) in healthy subjects, as well as a number of studies in combination with FXa inhibitors, including a Phase 1 study comparing the PK and PD of andexanet in younger vs. older subjects receiving apixaban (Study 14-506), the Phase 2 dose-range finding Study 12-502 (apixaban, rivaroxaban, edoxaban, and enoxaparin) and the confirmatory Phase 3 studies in healthy older subjects (50–75 years) with apixaban (Study 14-503) and rivaroxaban (Study 14-504), respectively. Summaries of these clinical studies are presented in the Investigator's Brochure.

1.4.1. Phase 1 Study of Andexanet Alone in Healthy Subjects

Study 11-501 was a Phase 1 randomized, double-blind, placebo-controlled study of the safety, PK, and PD of andexanet in 32 healthy subjects, each of whom received one of four doses of andexanet (30 mg, 90 mg, 300 mg, or 600 mg) (n=24) or placebo (n=8). The safety data from this study are summarized in Section 1.4.5.

1.4.2. Phase 1 Study of Andexanet in Healthy Younger versus Older Subjects

Study 14-506 was a Phase 1 non-randomized, open-label study of andexanet in healthy younger (18–45 years of age) subjects and healthy older (≥ 65 years of age) subjects. Ten younger and 10 older subjects were enrolled, with all subjects dosed to steady-state with apixaban then receiving a 400 mg bolus of andexanet. In this study, the PK of andexanet and the PD effects on anti-fXa activity and thrombin generation in older and younger subjects were similar.

1.4.3. Phase 2 Study of Andexanet with Factor Xa Inhibitors in Healthy Subjects

Study 12-502 was a Phase 2, randomized, double-blind, placebo-controlled study of the safety, PK, and PD of andexanet in healthy subjects receiving one of four direct or indirect FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin. Each FXa inhibitor was examined in a separate study module, within which multiple dosing regimens of andexanet are given in cohorts of 9 healthy subjects (6 active, 3 placebo). The anticoagulant was dosed to steady state over 5 to 6 days, before administration of andexanet or placebo on Study Day 6. Healthy subjects were then followed through Study Day 13 in a domiciled Phase 1 study unit and, subsequently, through Day 48 as outpatients.

Apixaban (Module 1) was administered at a dose of 5 mg orally (PO) twice each day for 5.5 days, rivaroxaban (Module 2) was administered at a dose of 20 mg PO once daily (QD) for 6 days, enoxaparin (Module 3) was administered at a dose of 40 mg subcutaneously (SQ) QD for 6 days, and edoxaban (Module 4) was administered at dose of 60 mg PO once daily. Andexanet was administered on Day 6, (typically 3 hours after the anticoagulant dose [C_{max}]).

The total dose of andexanet across dosing cohorts ranged from 90 mg to 1,760 mg. These cohorts included the evaluation of several dosing regimens: single bolus, double bolus, and bolus followed by a continuous infusion.

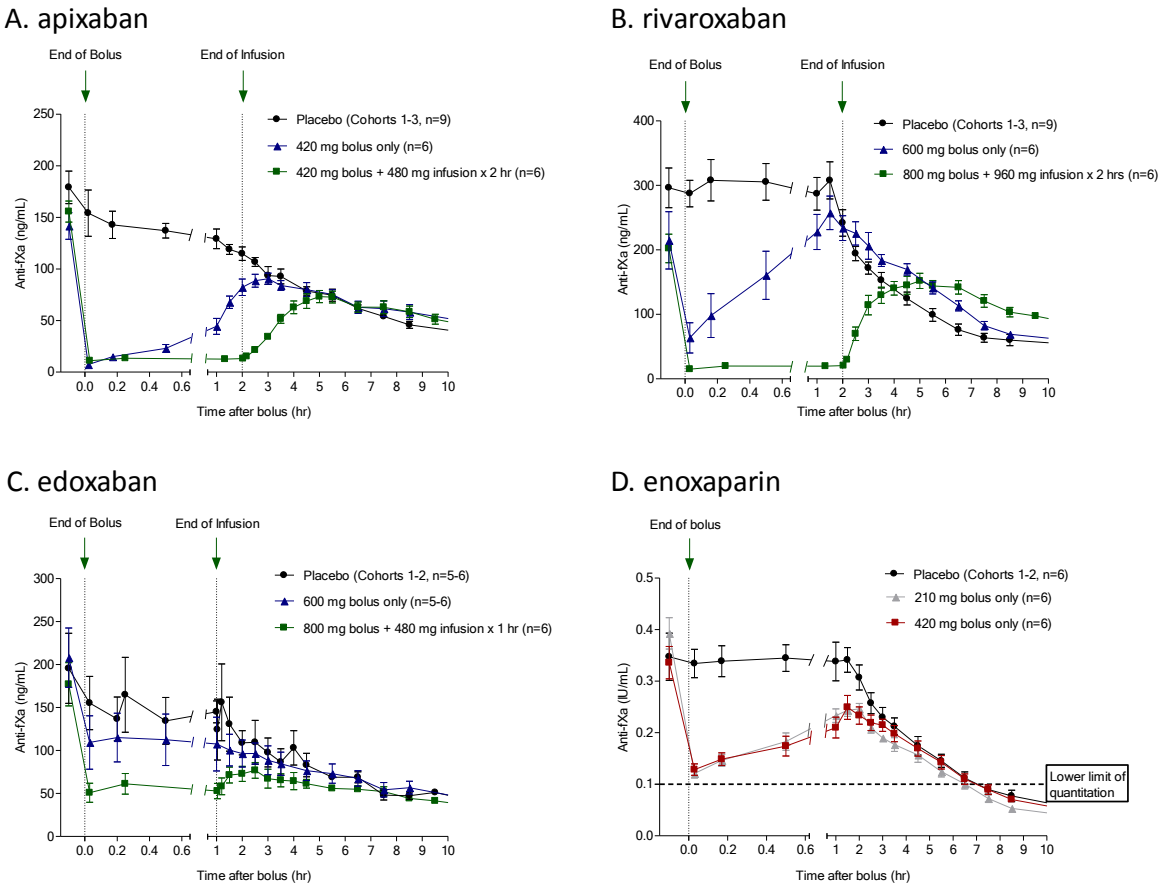
Andexanet exhibited dose-proportional PK for both C_{max} and area under the curve (AUC) with a mean terminal $t_{½}$ of approximately 5 hours and an effective (pharmacodynamic) $t_{½}$ of approximately 50 to 60 minutes.

For apixaban, rivaroxaban, edoxaban, and enoxaparin, administration of andexanet resulted in a dose-dependent reduction in anti-fXa activity (Figure 2). "Baseline" was defined as the time immediately prior to andexanet administration, which occurred 3 hours following the last anticoagulant dose (the anticoagulant steady-state C_{max}).

Administration of andexanet was associated with a rapid and immediate decrease in unbound apixaban, rivaroxaban, and edoxaban that was dose-dependent, with the greatest effect observed at the highest doses tested (420 mg dose for apixaban, and 800 mg dose for rivaroxaban and edoxaban). When andexanet was administered as a bolus followed by a continuous infusion, the decrease in unbound (free fraction) of apixaban, rivaroxaban, and edoxaban was sustained.

Additionally, apixaban, rivaroxaban, edoxaban, and enoxaparin inhibited thrombin generation relative to the pre-anticoagulant baseline (Study Day 1). These anticoagulant effects of apixaban, rivaroxaban, and edoxaban were reversed in a dose-dependent fashion by administration of andexanet. These effects are consistent with restoration of hemostatic mechanisms after andexanet administration. The safety data from this study are summarized in Section 1.4.5.

Figure 2: Rapid Onset and Reduction of Anti-fXa Activity (Study 12-502)



A. Apixaban was administered at 5 mg orally (PO) twice a day (BID) for 5.5 days; andexanet was administered on Day 6 as a 420 mg IV bolus or 420 mg IV bolus + 480 mg infusion (120 minutes at 4 mg/min).

B. Rivaroxaban was administered at 20 mg once daily (QD) for 6 days; andexanet was administered on Day 6 as either a 600 mg IV bolus or an 800 mg IV bolus + 960 mg infusion (120 minutes at 8 mg/min).

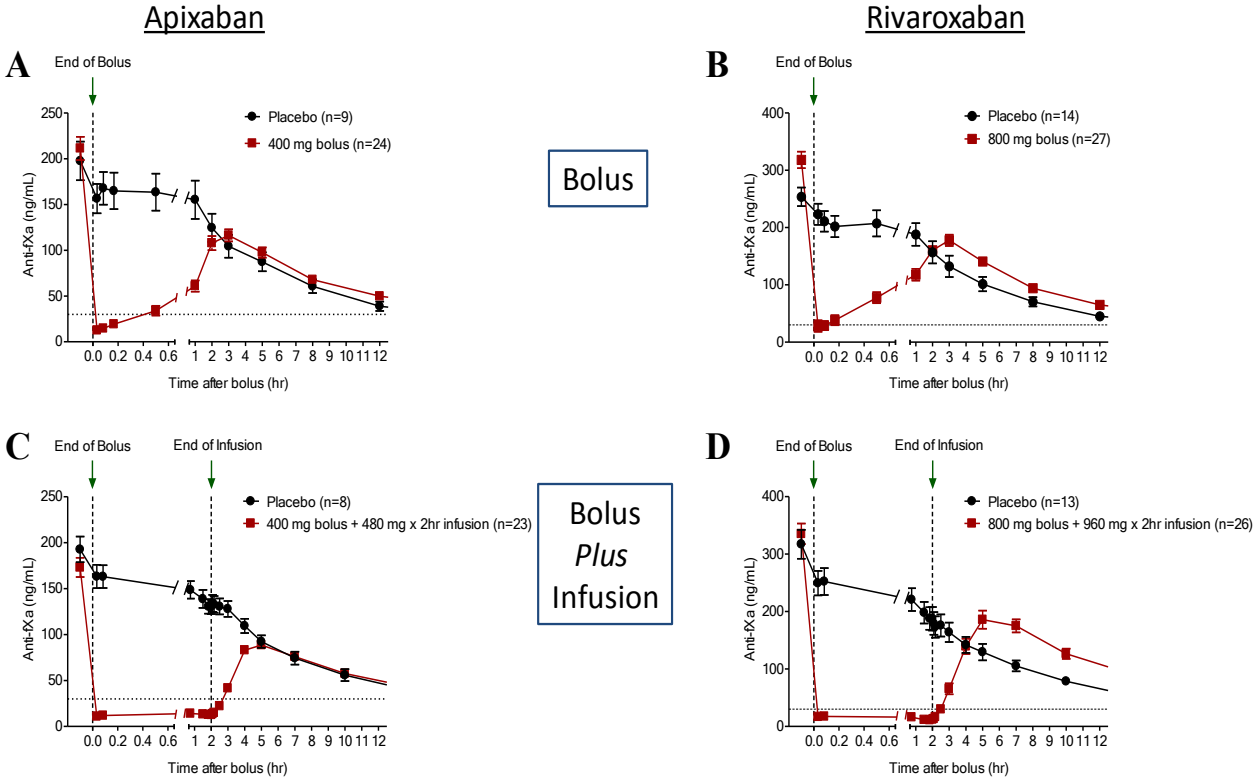
C. Edoxaban was administered at 60 mg once daily (QD) for 6 days; andexanet was administered on Day 6 as either a 600 mg IV bolus or an 800 mg IV bolus + 480 mg infusion (60 minutes at 8 mg/min).

D. Enoxaparin was administered at 40 mg subcutaneously (SQ) QD for 6 days; andexanet was administered on Day 6 as a 210 mg or 420 mg IV bolus. Andexanet administration was timed with the approximate steady-state Cmax of each anticoagulant (3 hours after the last dose). Data are shown as mean ± standard error of the mean (SEM).

1.4.4. Phase 3 Studies in Healthy Older Volunteers

Two randomized, double-blind, placebo-controlled studies were designed to evaluate reversal of anticoagulation in older subjects (ages 50–75 years) anticoagulated with apixaban (Study 14-503) or rivaroxaban (Study 14-504). In these studies, the anticoagulant was dosed to steady state over 4 days (rivaroxaban) or 3.5 days (apixaban) before administration of andexanet or placebo on Study Day 4. The subjects were then followed through Study Day 8 in a domiciled Phase 1 study unit and, subsequently, through Day 43 as outpatients. Andexanet was administered either as an IV bolus (Part 1, data available) or an IV bolus plus a continuous infusion for 120 minutes (Part 2). Reversal of anticoagulation was measured using anti-fXa activity, anticoagulant free fraction, thrombin generation, and other coagulation markers. A single IV bolus of andexanet rapidly and significantly reversed the anti-fXa activity of apixaban and rivaroxaban (Figure 3), reduced unbound apixaban and rivaroxaban concentrations, and restored normal thrombin generation. These effects were sustained by the follow-on infusion.

Figure 3: Rapid Onset and Significant Reduction of Apixaban and Rivaroxaban Anti-fXa Activity in Older Healthy Subjects by Andexanet (Study 14-504)



Legend: Anti-fXa activity was measured prior to and after andexanet or placebo administration on study Day 4. Dashed lines indicate the end of bolus or infusion.

A. Apixaban—with andexanet 400 mg IV bolus.

B. Rivaroxaban—with andexanet 800 mg IV bolus.

C. Apixaban—with andexanet 400 mg IV bolus plus 4 mg/minute infusion for 120 minutes.

D. Rivaroxaban—with andexanet 800 mg IV bolus plus 8 mg/minute infusion for 120 minutes.

Note: A break in the X axis was added to better visualize the immediate, short-term dynamics of anti-fXa activity following andexanet treatment. The points on the graph represent the mean anti-fXa activity level and error bars illustrate standard error. There was a statistically significant difference ($p < 0.05$) in the percent change of anti-fXa activity normalized to pre-bolus between andexanet and placebo until 2 hours after administration of bolus (Part 1) or infusion (Part 2). The horizontal dashed-line represents the anti-fXa activity at 30 ng/mL, the estimated non-effective level for FXa inhibition [6].

The results from the Phase 3 studies of apixaban and rivaroxaban were very similar to results obtained in the Phase 2 study, demonstrating the reproducibility of andexanet's ability to reverse inhibition of FXa activity. This reproducibility of the data allowed Portola to use PK-PD modeling to select doses of andexanet for reversal edoxaban and enoxaparin.

1.4.5. Summary of Safety from Clinical Studies of Healthy Subjects

Andexanet has been generally well tolerated in healthy volunteers in the Phase 1, 2, and 3 studies at the doses studied (i.e., total doses of 30 mg, 90 mg, 210 mg, 300 mg, 420 mg, 600 mg, 900 mg, 960 mg, and 1,760 mg) with no apparent pattern of safety signals with the exception of mild-moderate infusion reactions. A single Adverse Event (AE) (bilateral pneumonia) met Serious Adverse Event (SAE) criteria in the Phase 1 study. This SAE, which was deemed by the Investigator as unlikely to be related to andexanet, occurred 18 days after andexanet dosing in a subject treated at a dose of 30 mg. No severe or life-threatening AEs have been reported. No Thrombotic Events (TEs) have been reported in either the healthy volunteer studies. Infusion reactions have been mild to moderate in severity, do not appear to be dose dependent and have rarely required treatment (2 healthy subjects received one dose each of diphenhydramine). With the exception of two healthy subjects in the Phase 1 study who received a 90 mg dose of andexanet, infusion reactions have not led to premature discontinuation of andexanet at doses of up to 1,760 mg total dose. Therefore, to date, infusion reactions have not been dose-limiting.

Andexanet was associated with dose-dependent increases in F1+2, TAT, and D-dimer and with concomitant decrease in Tissue Factor Pathway Inhibitor (TFPI) activity, all of which reversed quickly after discontinuation of andexanet. These changes returned to baseline on average by 4 days after discontinuation of andexanet. These findings were not associated with a clinical TE in any subject. Compared with administration of andexanet alone (Study 11-501), the effects on F1+2, TAT, D-dimer, and TFPI were attenuated (all to a similar extent) in the presence of apixaban, rivaroxaban, enoxaparin, and edoxaban.

Among healthy subjects treated with andexanet, 12.1% developed low-titer non-neutralizing antibody to andexanet. However, there have been no neutralizing antibodies, nor antibodies to native FX or FXa.

1.4.6. Phase 3b Study in Patients with Acute Major Bleeding

Study 14-505 (ANNEXA-4) is an ongoing, multi-national, prospective, open-label, single-arm clinical study of andexanet in patients with acute major bleeding while taking a factor Xa inhibitor (specifically apixaban, edoxaban, enoxaparin, and rivaroxaban). As of 09 June 2016, 57 patients with complete safety data had been enrolled in the study. Baseline characteristics included a median age of 80 years, 51% female, 81% Caucasian, and median BMI 27.2 kg/m^2. Twenty-six patients (46%) had gastrointestinal or urinary bleeding, 23 patients (40%) had an intracranial hemorrhage, and 8 patients (14%) had other types of bleeding.

Of the 57 patients with complete safety data, 30 (53%) experienced a total of 72 treatment emergent AEs. The most frequently reported AEs (occurring in ≥ 2% of subjects) by preferred term were deep vein thrombosis in 4 patients (7.0%); pneumonia, headache, and respiratory failure in 3 patients each (5.3%); and cardiogenic shock, sepsis, and pulmonary embolism in 2 patients each (3.5%). Two AEs (2.8%) were considered by the investigator to be possibly or

probably related to andexanet. Eighteen patients (25%) experienced a total of 36 treatment emergent SAEs. The most common SAEs (occurring in ≥ 2% of subjects) were cardiogenic shock (fatal) in 2 patients (3.5%), pulmonary embolism (severe) in 2 patients (3.5%), and respiratory failure (severe) in 2 patients (3.5%). One SAE (ischemic stroke) was assessed as probably related to andexanet.

There were 8 deaths (14%) in the study. The cause of most deaths (75%; 6/8) were non-cardiovascular and included respiratory failure in 2 patients, accident/trauma in 1 patient, bleeding in 1 patient, and other/non-vascular cause in 1 patient. In addition, 7 patients (12%) experienced an adjudicated clinical thromboembolic event (3 deep vein thromboses, 1 acute myocardial infarction, 1 cerebral infarction, 1 embolic stroke, 1 ischemic stroke). Importantly, of the 7 patients with a thromboembolic event, only 2 had been reanticoagulated prior to the event. There were no reported re-bleeding events in the study.

No clinically meaningful changes in laboratory values (including hematocrit and hemoglobin) were detected in the study. Similarly, no changes in vital signs and/or physical exam findings have been observed. Finally, 5 patients (8.8%) developed non-neutralizing antibodies to andexanet after 30 days of follow up. However, as in the healthy subjects treated with andexanet, no neutralizing antibodies have been detected to andexanet.

1.5. Rationale for Present Study

Though andexanet has been studied extensively in clinical trials, most subjects enrolled in these studies have been Caucasian. While there is no a priori reason to expect racial and/or ethnic differences in the efficacy, safety, and PK profiles for protein therapeutics, potential differences with andexanet have not been tested clinically. The present study therefore aims to evaluate for such potential differences. In this study, the efficacy of andexanet to reverse FXa inhibitor-induced anticoagulation, and the safety of andexanet in this context, will be evaluated in individuals of Japanese descent. In addition, the PK and PD of andexanet in Japanese subjects dosed to steady-state with apixaban will be evaluated and compared to a parallel cohort of Caucasian subjects dosed to steady-state with apixaban.

2.0 STUDY OBJECTIVES

The objectives of this study are to assess the following in healthy subjects dosed to steady state with direct oral FXa inhibitors (apixaban, rivaroxaban, and edoxaban):

Primary Efficacy Objective

- To compare andexanet and placebo with respect to reversal of each FXa inhibitor as measured by anti-fXa activity.

Secondary Efficacy Objectives

- To assess andexanet and placebo with respect to reversal of each FXa inhibitor as measured by free fraction of the inhibitor.
- To assess andexanet and placebo with respect to reversal of each FXa inhibitor as measured by restoration of thrombin generation.
- To assess the pharmacodynamics of andexanet in Japanese subjects and Caucasian subjects, as measured by anti-fXa activity, free fraction of the FXa inhibitor (apixaban), and restoration of thrombin generation.

Safety Objective

- To evaluate the safety of andexanet in Japanese subjects.

Pharmacokinetics Objectives

- To evaluate the pharmacokinetics of andexanet in Japanese subjects.
- To compare the pharmacokinetics of andexanet in Japanese subjects to the pharmacokinetics of andexanet in Caucasian subjects.

3.0 INVESTIGATIONAL PLAN

3.1. Study Design

This is a single-center, randomized, double blind, and placebo-controlled trial designed to evaluate the efficacy, safety, and PK-PD of andexanet in healthy Japanese subjects taking direct FXa inhibitors at therapeutic doses. Reversal of anticoagulation will be evaluated by measuring anti-fXa activity, unbound FXa inhibitor plasma levels, and thrombin generation.

A total of 10 cohorts of approximately 9 to 12 evaluable subjects (6–8 active, 3–4 placebo) in Part 1, and 9 to 15 evaluable subjects (6-10 active, 3-5 placebo) in Part 2 will be studied in two parts (Table 1):

- Part 1 will evaluate the efficacy (as assessed by FXa inhibitor reversal), safety, and PK of andexanet in Japanese subjects, and evaluate for similarities between analogous data from Caucasian subjects.
- Part 2 will evaluate andexanet reversal effect of FXa inhibitor with additional dosing regimens. The dosing regimens in Part 2 were informed by the preliminary results of Part 1.

Table 1: Cohort Details

Part 1 Cohorts			
Cohort	**FXa Inhibitor**	**Andexanet**	**N (Active/Placebo)**
1	Apixaban 5 mg BID	400 mg bolus + 4 mg/min 120 min infusion/placebo (andexanet dosing at 3 hours post-apixaban)	Japanese 9 (6/3)
2	Rivaroxaban 15 mg BID	800 mg bolus + 8 mg/min 120 min infusion/placebo (andexanet dosing at 4 hours post-rivaroxaban)	Japanese 9 (6/3)
3	Edoxaban 60 mg QD	800 mg bolus + 8 mg/min 120 min infusion/placebo (andexanet dosing at 3 hours post-edoxaban)	Japanese 12 (8/4)
4	Edoxaban 60 mg QD	800 mg bolus + 8 mg/min 120 min infusion/placebo (andexanet dosing at 90 minutes post-edoxaban)	Japanese 12 (8/4)
5	Apixaban 5 mg BID	400 mg bolus + 4 mg/min 120 min infusion/placebo (andexanet dosing at 3 hours post-apixaban)	Caucasian 9 (6/3)
Part 2 Cohorts			
6	Apixaban 10 mg BID	800 mg bolus + 8 mg/min 120 min infusion/placebo (andexanet dosing at 3 hours post apixaban)	Japanese 9 (6/3)
7	Edoxaban 30 mg QD	400 mg bolus + 4 mg/min 120 min infusion/placebo (andexanet dosing at 90 min post edoxaban)	Japanese 12 (8/4)
8	Apixaban 10 mg BID	400 mg bolus + 4 mg/min 120 min infusion/placebo (andexanet dosing at 8 hours post apixaban)	Japanese 9 (6/3)
9	Rivaroxaban 15 mg BID	400 mg bolus + 4 mg/min 120 min infusion/placebo (andexanet dosing at 8 hours post rivaroxaban)	Japanese 15 (10/5)
10	Edoxaban 60 mg QD	400 mg bolus + 4 mg/min 120 min infusion/placebo (andexanet dosing at 8 hours post edoxaban)	Japanese 12 (8/4)

BID = Twice a day; FXa = Factor Xa; QD = Once daily

Following screening, study subjects will be randomized and domiciled at the study site for ~10 days, during which time they will be administered apixaban 5 or 10 mg PO BID, rivaroxaban 15 mg PO BID, or edoxaban 30 or 60 mg PO QD (depending on cohort; see above) on Days 1 to 6. Andexanet or matching placebo bolus and continuous infusion doses will be administered on Day 6, at various times after the last administration of FXa inhibitor. Study subjects will be discharged from the clinical site on Day 10 and followed for safety through Day 36 (+3).

The primary endpoint is the difference in the percent change from baseline anti-fXa activity between andexanet- and placebo-treated subjects in each cohort. That is, i.e., the percent change from baseline (where baseline is the time point immediately prior to the administration of andexanet) in anti-fXa activity to its nadir. The nadir is defined as the smallest value for anti-fXa activity between the 110-minute time point (10 minutes prior to the end of the continuous andexanet infusion) and the 5-minute time point after the end of the continuous infusion (inclusive).

For all cohorts, subjects will be randomized at a 2:1 ratio to treatment with andexanet or placebo, respectively. If enrolled subjects discontinue early from the study or have missing data for any reason, the Sponsor may elect to add up to 3 additional subjects (with newly blinded treatment assignments) within the discontinued subject's assigned cohort.

To compare the PK-PD of andexanet between Japanese and Caucasian subjects, the results of Cohorts 1 (Japanese only) and 5 (Caucasian only) will be evaluated in context with each other.

The number of subjects expected to enroll in this study is approximately 108 evaluable subjects across all 10 cohorts. The Sponsor may also elect to end enrollment early if, for example, an acceptable number of evaluable subjects is achieved. Each subject will participate in only one andexanet dosing regimen and will be domiciled for 10 days, during which time they will be dosed to steady state (up to 6 days) on the anticoagulant and then followed for 3 days after receiving andexanet. Blood and urine samples will be obtained according to a pre-determined schedule. Regular clinical examinations will be conducted throughout the study.

3.2. Blinding and Randomization

3.2.1. Randomization

In all cohorts, subjects will be randomized in a 2:1 ratio to receive andexanet or placebo, respectively, using permuted blocks. The randomization code will be generated and maintained by a Contract Research Organization (CRO). Subjects will be randomized on Day 1, at which time the unblinded research pharmacist or designee will obtain the subject's treatment assignment. If subjects are added to a given cohort in the event of an early study discontinuation or missing data, they will be newly randomized by the procedure described above (as opposed to being given the same treatment assignment as the discontinued subject).

3.2.2. Blinding

Within each cohort, each FXa inhibitor will be administered to all subjects and therefore no blinding is required for the FXa inhibitor. Andexanet or its placebo will be administered to subjects in a double-blind fashion using a randomization schedule provided by the CRO. The unblinded dispensing pharmacist or designated qualified individual may unblind a subject in an emergency or at the request of the PI or Medical Monitor to determine if the subject received active drug. In that event, the Sponsor's Medical Monitor must be immediately notified. A subsequent written report, including all pertinent details, must be submitted to the Sponsor's Medical Monitor.

3.2.3. Unblinding

The blind is to be strictly maintained. However, in the event of a medical emergency for which the treatment assignment needs to be known in order to manage the subject, the blind may be broken by the Investigator or qualified designee. The Investigator must make every effort to contact the Sponsor's Medical Monitor prior to unblinding a subject, unless the emergent nature

of the situation precludes this communication. The Investigator must notify the Medical Monitor as soon as possible if the blind is broken for any reason. A subsequent written report, including all pertinent details, must be submitted to the Medical Monitor.

3.3. Duration of Study

For each individual subject, the study duration will be approximately 6–12 weeks, depending on the length of Screening. The study periods are as follows:

- Screening: Days -45 to -1
- Anticoagulant Dosing: Days 1 to 6
- Andexanet Dosing: Day 6
- Safety Follow-Up: Days 7 to 36 (+3)

Study subjects will be domiciled from Day -1 to Day 10, and then discharged from the inpatient facility on Day 10 to continue outpatient follow-up through Day 36 (+3).

3.4. Factor Xa Inhibitor and Andexanet Dosing Considerations

The doses of FXa inhibitors used in the study are currently approved doses used in most patients. As such, these doses are not expected to pose any significant safety risk to a healthy subject population. Additionally, andexanet doses of up to an 800 mg bolus and 960 mg infusion over 120 minutes have been studied previously in healthy subjects and were well tolerated. Importantly, FXa inhibitors and andexanet have been used concurrently at the doses used in the study in prior studies of healthy volunteers (12-502, 14-503, 14-504); no safety concerns have arisen during the conduct of these studies.

3.5. Safety Plan and Monitoring

While this type of study is typically designed as a 2-period crossover trial, a parallel group design is used in this case in order to minimize the risk of antigenicity in healthy subjects. Furthermore, to monitor for immunogenicity, blood specimens will be serially evaluated at each outpatient follow-up visit (Days 20 and 36) for antibodies against andexanet and against FX and FXa. Samples that are positive for antibodies to andexanet will be further assayed for the ability to neutralize the activity of andexanet. Samples at specific time points will be tested for potential neutralizing antibody activity against FX or FXa using a modified Bethesda assay.

Subjects will be monitored while domiciled in the clinical site for the entire period that they are anticoagulated with FXa inhibitors and for 3 days after administration of andexanet. Although there have been no thromboembolic events in any healthy subjects dosed with andexanet thus far, some pro-thrombotic markers (D-dimer, F1+2, and TAT) increase following andexanet infusion, generally resolving within 4 days after treatment. This increase is typically diminished when andexanet is co-administered with an FXa inhibitor, as will be the case in the present study. D-dimer, F1+2, and TAT will be obtained and reviewed in the present study.

Furthermore, a clinical assessment of venous thromboembolism risk (via Wells scoring) will be performed at multiple time points during the study.

Prior and ongoing clinical studies have identified infusion reactions of mild or moderate intensity as the most common adverse event related to administration of andexanet. Although no severe or serious infusion reactions have occurred to date in healthy subjects receiving andexanet, subjects in this study will receive andexanet in an inpatient, monitored setting under medical supervision and immediate access to resuscitative measures. Notably, infusion reactions observed in prior and ongoing studies have had their onset during the infusion itself. Therefore, in addition to vital signs, oxygen saturation will be monitored during the infusion.

To monitor for occult bleeding, stool occult blood testing will be performed on any stool samples produced throughout the period subjects are domiciled. The relatively short $t_{½}$ of all FXa inhibitors predicts a loss of anticoagulant effects within one day of the end of treatment. Following discharge from the clinical site, subjects will return for follow-up on Days 20 and 36 for safety follow-up.

Finally, safety data will be reviewed by the Sponsor on an ongoing basis.

4.0 SELECTION OF SUBJECTS

Men and women with an unremarkable medical history, physical examination, and routine clinical laboratory results will be selected for screening for this study.

To be eligible for study enrollment, subjects must satisfy the following inclusion and exclusion criteria:

4.1. Inclusion Criteria

1. Must be in reasonably good health as determined by the Investigator based on medical history, full physical examination (including blood pressure and pulse rate measurement), 12-lead ECG, and clinical laboratory tests. Subjects with well-controlled, chronic, stable conditions (e.g., controlled hypertension, non-insulin dependent diabetes, osteoarthritis, hypothyroidism) may be enrolled based on the clinical judgment of the Investigator.
2. For all cohorts except Cohort 5, subjects must be Japanese, defined as having four ethnic Japanese grandparents. Subjects may not have lived outside of Japan for more than 10 years. Subjects in Cohort 5 must be of Caucasian race.
3. Must be between the ages of 18 and 75 years, inclusive, at the time of signing of the Informed Consent Form (ICF).
4. Agrees to have any dietary or nutritional supplements reviewed by the Investigator and potentially held during the study if advised by the Investigator. Standard multivitamin and mineral supplementation will be permitted.
5. Agrees to comply with the contraception and reproduction restrictions of the study:
    - Men whose sexual partner is of childbearing potential and/or who are not monogamous must be using two acceptable methods of contraception, at least one of which must be a barrier method (e.g., spermicidal gel plus condom), for the entire duration of the study and for at least 1 month following study-drug administration; and men must refrain from attempting to father a child or donating sperm in the 1 month following the study-drug administration. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Men who report surgical sterilization (e.g., bilateral vasectomy) must have had the procedure at least 6 months before study drug administration.
    - Surgical sterilization procedures should be supported with clinical documentation and noted in the Relevant Medical History/Current Medical Conditions section of the Case Report Forms (CRFs).

- Women of childbearing potential must be using two medically acceptable methods of contraception, at least one of which must be a barrier method (e.g., non-hormone containing intra-uterine device plus condom, spermicidal gel plus condom, diaphragm plus condom),

from the time of Screening and for the duration of the study, through at least 1 month following study drug administration. NOTE: Oral and topical hormonal contraceptive use, as well as the use of hormone-containing intra-uterine devices, is not permitted due to their increased risk of thromboembolism. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception;

OR

- Postmenopausal women must have had no regular menstrual bleeding for at least 1 year before initial dosing and either be over the age of 60 years or have an elevated plasma follicle-stimulating hormone (FSH) level (i.e., > 40 mIU/mL) at Screening;

OR

- Women who report surgical sterilization (i.e., hysterectomy, tubal ligation, and/or bilateral oophorectomy) must have had the procedure at least 6 months before study drug administration. Surgical sterilization procedures should be supported with clinical documentation and noted in the Relevant Medical History/Current Medical Conditions section of the CRF;

AND

- All female subjects must have a documented negative pregnancy test result at Screening and on Study Day -1.

6. Systolic blood pressure < 160 mmHg and diastolic blood pressure < 90 mmHg at Screening and Day -1.
7. The following laboratory values must be within the normal laboratory reference range within 45 days of Day -1: PT, aPTT, and ACT; Hemoglobin, hematocrit, and platelet count.
8. The following laboratory values must be equal to or below 2 times the upper limit of normal (ULN) range within 45 days of Day -1: Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) and total bilirubin.
9. The Screening serum creatinine must be below 1.5 mg/dL within 45 days of Day -1.
10. Body mass index of less than 30 kg/m^2, inclusive, and body weight between 50 to 80 kg, inclusive, at Screening. Subjects in Cohorts 3, 4, and 10 must be at least 60 kg in weight.
11. Agrees to abstain from alcohol consumption for the duration of the domicile period, and from the use of drugs of abuse for the duration of the study.
12. Able to read and give written informed consent and has signed a consent form approved by the Investigator's Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

4.2. Exclusion Criteria

1. Previous use of andexanet or previous participation in the current study (even if the subject received placebo).
2. History of abnormal bleeding, signs or symptoms of active bleeding, or risk factors for bleeding.
3. Has a stool specimen that was positive for occult blood within 6 months of study Screening or during the Screening Period.
4. Past or current medical history of thrombosis, any sign or symptom that suggests an increased risk of a systemic thrombotic condition or thrombotic event, or recent events that may increase risk of thrombosis.
    a. For example, subjects with a known or suspected hypercoagulable state, history of VTE, DVT, stroke, myocardial infarction [MI], cancer [other than non-melanoma skin cancer], atrial fibrillation, heart failure, cardiomyopathy, phlebitis, lower extremity edema, major surgery or trauma within 2 months of Study Day -1, airplane travel with a planned flight time for any single flight segment $\geq$ 6 hours during the 4 weeks prior to Study Day -1, or general immobility are excluded.
5. Absolute or relative contraindication to anticoagulation or treatment with apixaban, rivaroxaban, and/or edoxaban.
6. Prior consumption (by any route) of one or more doses of aspirin (including baby aspirin), salicylate or subsalicylate, other antiplatelet drugs (e.g., ticlopidine, clopidogrel), non-steroidal anti-inflammatory drugs, fibrinolytic, or any anticoagulant within 7 days prior to Day -1 or is anticipated to require such drugs during the study.
7. Receipt of (by any route) hormonal contraception, post-menopausal hormone replacement therapy (HRT) (including over-the-counter products), or testosterone during the 4 weeks prior to Study Day -1 or is anticipated to require such drugs during the study.
8. Family history of or risk factors for a hypercoagulable or thrombotic condition, including one of the following:
    a. Factor V Leiden carrier or homozygote;
    b. Protein C, S, or ATIII activity below the normal range.
9. History of adult asthma or chronic obstructive pulmonary disease or current regular or as-needed use of inhaled medications.
10. Active HBV, HCV, or HIV-1/2 infection.
11. Use of any drugs that are strong dual inhibitors or inducers of CYP3A4 (apixaban and rivaroxaban cohorts only) and P-gp (all cohorts) within 7 days prior to Study Day -1 or anticipated need for such drugs during the study.
12. Participation in an investigational drug study within 45 days of Day -1 or Day -1 is within 5 half-lives of the investigational compound.

13. Positive screen for drugs of abuse at Day -1 that is not explained by a prescription medication that the subject is known to be taking.
14. A medical or surgical condition that may impair drug (anticoagulant or andexanet) metabolism.
15. Allergy to any of the vehicle ingredients: tris, arginine, sucrose, hydrochloric acid, mannitol, and polysorbate 80.
16. Allergy to soy or soy products.
17. Current breastfeeding or a positive pregnancy test at Screening or Day -1.
18. Any condition that could interfere with, or for which the treatment might interfere with, the conduct of the study or interpretation of the study results, or that would in the opinion of the Investigator increase the risk of the subject's participation in the study. This would include but is not limited to alcoholism, drug dependency or abuse, psychiatric disease, epilepsy, or any unexplained blackouts.
19. The subject is not judged by the study staff to have adequate bilateral venous access.
20. Unwillingness to adhere to the activity requirements of the study.

4.3. Subject Replacement

No subject will be replaced (i.e., no subjects' data will be excluded from analysis). If a subject discontinues the study early or otherwise has missing data, up to 3 additional subjects per cohort may be added at the discretion of the Sponsor to ensure evaluability of the study endpoints.

5.0 STUDY MATERIALS AND DOSING

5.1. Clinical Supplies, Formulation, and Storage

5.1.1. Andexanet

Andexanet for Injection (200 mg/vial) is supplied by Portola Pharmaceuticals, Inc. as a lyophilized product for reconstitution for IV injection. The labeled storage condition is refrigerated (i.e., 2–8°C). The lyophilized product needs to be reconstituted using Sterile Water for Injection before use. For details on reconstituting/preparing andexanet, please refer to the Pharmacy Manual.

5.1.2. Placebo (Vehicle Control)

Lyophilized placebo product (100 mg/vial) with the same appearance and container closure and containing all ingredients in the active product except andexanet will serve as the placebo control.

5.1.3. Apixaban

Apixaban is an approved product in Europe, Japan, and the United States. Apixaban (5 mg tablets) will be obtained by the Contract Research Organization (CRO) from commercial supply. Apixaban should be stored according to the instructions in the apixaban (Eliquis®) US package insert (Appendix D). For additional information on the 5 mg tablets, see the apixaban US package insert.

5.1.4. Edoxaban

Edoxaban is an approved product in Europe, Japan, and the United States. Edoxaban (30 and 60 mg tablets) will be obtained by the CRO from commercial supply. Edoxaban should be stored according to the instructions in the edoxaban (Savaysa®) US package insert (Appendix E). For additional information on the 30 and 60 mg tablets, see the edoxaban US package insert.

5.1.5. Rivaroxaban

Rivaroxaban is an approved product in Europe, Japan, and the United States. Rivaroxaban (15 mg tablets) will be obtained by the CRO from commercial supply. Rivaroxaban should be stored according to the instructions in the rivaroxaban (Xarelto®) package insert (Appendix F). For additional information on the 15 mg tablets, see the rivaroxaban US package insert.

5.2. Dispensing of Study Medication (Factor Xa Inhibitors and Andexanet)

The dispensing pharmacist or designated qualified individual will write the date dispensed, dose dispensed, and the subject's identification number or initials on the Drug Accountability Source Documents. All used medication supplies and/or partially used drug supplies will be destroyed at the site in accordance with approved written site procedures, or returned to the Sponsor only after written authorization is obtained from the Sponsor. The Investigator will maintain a record

of the amount and dates when unused supplies were either destroyed or returned to the Sponsor. All records will be retained as noted in Section 10.11.

5.3. Factor Xa Inhibitor Dosing

All FXa inhibitors will be administered open label. FXa inhibitors will be administered for 6 days, and according to the following dosing schedule:

- Cohorts 1, 5, 6, and 8 (apixaban): 5 mg or 10 mg orally, every 12 hours, fasted; last dose morning of Day 6
- Cohorts 2 and 9 (rivaroxaban): 15 mg orally, every 12 hours, with food; last dose morning of Day 6
- Cohorts 3, 4, 7, and 10 (edoxaban): 30 mg or 60 mg orally, once daily, in the morning, fasted; last dose morning of Day 6

5.3.1. Factor Xa Inhibitor Dosing—Fed/Fasting Conditions

For Cohorts 1, 5, 6, and 8 (apixaban) subjects will fast (i.e., nothing by mouth except water) for at least 8 hours before and 2 hours after the AM dose of apixaban. A standard breakfast will be served ~2 hours after the morning apixaban dose. A standard lunch will be served ~4 hours after the AM dose. A standard dinner will be served ~8 hours after the morning dose and a standard light snack may be served ~1 hour after the PM dose of apixaban. Subjects are required to fast for at least 3 hours prior to the PM dose of apixaban. On the day of andexanet dosing, the timing of lunch may be moved to after the infusion for cohorts with an extended continuous infusion.

For Cohorts 2 and 9 (rivaroxaban), subjects will be administered rivaroxaban in the fed state, using a meal calendar that is the same for all subjects within the cohort.

For Cohorts 3, 4, 7, and 10 (edoxaban), subjects will fast (i.e., nothing by mouth except water) for at least 8 hours before and 2 hours after the dose of edoxaban. A standard breakfast will be served ~2 hours after the edoxaban dose. A standard lunch will be served ~4 hours after the dose. A standard dinner will be served ~8 hours after the dose of edoxaban. On the day of andexanet dosing, the timing of lunch may be moved to after the infusion for cohorts with an extended continuous infusion.

All FXa inhibitors will be administered with 240 mL of water.

5.4. Andexanet Dosing

Table 2 outlines the dosing specifications for each cohort.

In Cohorts 1, 5, 7, 8, 9, and 10, andexanet 400 mg or its placebo equivalent will be administered as a slow IV bolus at a target rate of approximately 30 mg/min starting 3 hours or 8 hours after the last dose of FXa inhibitor, followed by a continuous infusion at a rate of approximately 4 mg/min for 120 minutes (480 mg).

In Cohorts 2, 3, 4, and 6, andexanet 800 mg or its placebo will be administered as a slow IV bolus at a target rate of approximately 30 mg/min starting 1.5, 3, or 4 hours after the last dose of FXa inhibitor, followed by a continuous infusion at a rate of approximately 8 mg/min for 120 minutes (960 mg).

Table 2: Dosing Specifications by Test Product and Cohort

Cohort	Test Product	Dose/Mode of Administration
1, 5, 7, 8, 9, 10	Andexanet 200 mg vial	400 mg bolus + 4 mg/min 120 minute infusion IV
2, 3, 4, 6	Andexanet 200 mg vial	800 mg bolus + 8 mg/min 120 minute infusion IV
Reference Therapy		
All	Reference therapy Placebo 100 mg vial	Placebo 400 or 800 mg bolus, + 4 or 8 mg/min 120 minute infusion IV

IV = Intravenous

5.5. Dietary Restrictions

No alcohol may be consumed 48 hours prior to dosing and during the in-house period. Meals will be identical for all subjects and will be provided at the same time relative to dosing each day during the treatment period and per clinic protocol. Identical meals will be served on respective days of each treatment period. Smoking must be restricted to < 4 cigarettes/day (or equivalent).

5.6. Concomitant Medications

The use of any prescription, over-the-counter, or herbal medication (including oral contraceptives) during study conduct, especially during the domiciled portion of the study, is prohibited. Acetaminophen may be used at a maximum dose of 2 g/day at the discretion of the Investigator, however. If it is medically necessary to initiate any concomitant medications during the course of the study, they will be recorded on the appropriate CRF and the Sponsor's Medical Monitor must be notified within 24 hours of initiation. The eligibility of any subject who receives a concomitant medication other than acetaminophen to continue in the study will be determined. All medications taken within 30 days of the study entry will be recorded on the appropriate CRF.

6.0 ENROLLMENT AND STUDY PROCEDURES

Subjects will be considered enrolled into the study once they have signed the ICF and satisfied all inclusion and exclusion criteria. At this time, subjects will be assigned a subject identification number. The study duration for any individual subject will be up to 65 days, including a screening period of up to 45 days, an in-house stay at the clinical site of 10 days and a follow-up period of up to 27 days after discharge. A detailed description of the subject visits and clinical evaluations can be found in Appendix B: Schedule of Activities (Part 1) and Appendix B: Schedule of Activities (Part 2).

At time points when phlebotomy coincides with vital sign determinations and other activities, priority should be given to obtaining the PK sample as precisely at the due time as possible. All vital signs will be collected in the sitting position (after 5 minutes). In addition to fecal occult blood testing at Day -1, stool will be tested daily (if produced) during the domiciled portion for fecal occult blood.

With respect to intravenous access there are several important considerations:

1. A peripheral IV line may be used for PK sampling, however, this line should be in the opposite arm.
2. If obtaining PK specimens through a peripheral IV line, it should be through a dedicated IV line. That is, PK samples should not be drawn from IVs used to administer study drug.

In accordance with good clinical practice, any AEs or clinically significant abnormal laboratory results will be followed until resolved or stabilized.

6.1. Screening Visit Procedures (Days -45 to -2)

This visit to the study facility will take place within 45 days of the first dosing day, and may be performed on more than one day.

- Obtain written informed consent.
- Review inclusion/exclusion criteria.
- Obtain, review, and record medical history.
- Record medication history over last 30 days (including prescription drugs, over-the-counter medications, supplements, and herbal products).
- Obtain height, weight, and vital signs: blood pressure (BP), respiratory rate (RR), heart rate (HR), and temperature (sitting) (see Section 7.5.1).
- Obtain a 12-lead ECG (record electronically) and record the Investigator's reading (See Section 7.5.5).

- Collect local laboratory samples and urinalysis (see Appendix B, Appendix B and Section 7.2.2, Section 7.5.7, and Section 7.5.8); Local laboratory samples must be drawn within 45 days of Day -1.
- Confirm negative serum pregnancy test for women and verify FSH is in the postmenopausal range, if applicable (see Section 7.2.3).
- Test stool samples submitted by subject for occult blood (see Section 7.5.6).
- Instruct subjects regarding the alcohol restrictions and contraception requirements.
- Instruct subjects on dietary restrictions related to fecal occult blood testing, and provide them with 3 stool testing cards to return at any time during the Screening period or Day -1. Only 1 stool specimen submitted for fecal occult blood testing is required prior to Day 1; the 3 testing cards are provided for convenience purposes.
- Assess clinical thromboembolic risk.
- If screened over multiple visits, record AEs since most recent visit, starting with the second visit.

6.2. Rescreening Procedures

A subject may be rescreened on a case-by-case basis, provided that they fulfill all eligibility criteria at the time of rescreening, with the prior written approval of the Investigator and the Medical Monitor. If a subject is rescreened, the following procedures should be performed/repeated during the Rescreening Visit:

- Review inclusion/exclusion criteria.
- Review medical history and record changes since prior Screening Visit.
- Record medication history and record changes since prior Screening Visit.
- Perform physical examination.
- Obtain height, weight, and vital signs: Blood Pressure (BP), Respiratory Rate (RR), Heart Rate (HR), and temperature (sitting) (see Section 7.5.1).
- Obtain a 12-lead ECG (record electronically) and record the Investigator's reading (see Section 7.5.5).
- Collect local laboratory samples and urinalysis (see Appendix B, Appendix B and Section 7.2.3, Section 7.5.7, and Section 7.5.8); local laboratory samples must be drawn within 28 days of Day -1. Hepatitis B and C, HIV 1 and 2, Factor V Leiden, Protein C and S, and antithrombin III testing does not need to be repeated.
- Test stool samples submitted by the subject for occult blood (see Section 7.5.6).
- Instruct subjects regarding the alcohol restrictions and contraception requirements.

- Instruct subjects on dietary restrictions related to fecal occult blood testing, and provide then with 3 stool testing cards to return at any time during the Screening period or Day -1. Only 1 stool specimen submitted for fecal occult blood testing is required prior to Day 1; the 3 testing cards are provided for convenience purposes.
- Assess clinical thromboembolic risk.
- If screened over multiple visits, record AEs since most recent screening visit, starting with the second visit.

6.3. Day -1 (Admission Day) Procedures

- Admit the subject to the inpatient facility.
- Review eligibility requirements, including any changes.
- Perform a physical examination (see Section 7.5.2) and clinical VTE screening (see Section 7.5.3).
- Obtain vital signs (BP, HR, RR, and temperature) (sitting).
- Collect local and central laboratory samples and urinalysis (see Appendix B, Appendix B).
- Confirm negative drugs of abuse/breathalyzer screen (see Section 7.2.1 Section 7.2.2).
- Confirm negative serum pregnancy test for women.
- Record concomitant medications.
- Test stool samples submitted by subject for occult blood (if not already completed at Screening).
- Assess clinical thromboembolic risk.
- Serve standardized meals at fixed times (see Section 5.5).
- Record AEs that occurred since most recent screening visit.

6.4. Factor Xa Inhibitor Dosing Period (Days 1–5)

6.4.1. Day 1

Prior to the morning dose of FXa inhibitor:

- Obtain vital signs within 90 minutes before FXa inhibitor administration.
- Collect central laboratory samples within 90 minutes before FXa inhibitor administration (see Appendix B, Appendix B).
- Test stool samples submitted by subject for occult blood (if produced).
- Once the above procedures are completed, administer the morning dose of FXa inhibitor.

- For apixaban and rivaroxaban cohorts, administer the evening dose of apixaban and rivaroxaban approximately 12 hours after the morning dose.
- Standardized meals are to be served at fixed times in relation to FXa inhibitor dosing; please note that these times may occur before or after dosing, depending on the identity of the inhibitor.
- Concomitant medications and AEs should be recorded periodically throughout the day.

6.4.2. Days 2 to 4

- Obtain vital signs within 90 minutes before FXa inhibitor administration.
- Collect F1+2, TAT, D-dimer, and TFPI activity samples within 5 minutes before FXa inhibitor administration (see Appendix B, Appendix B). TFPI (total and free antigen) collected in Part 1 only.
- Test stool samples submitted by subject for occult blood (if produced).
- Administer the morning dose of FXa inhibitor.
- For apixaban and rivaroxaban cohorts, administer the evening dose of apixaban and rivaroxaban approximately 12 hours after the morning dose.
- Standardized meals are to be served at fixed times in relation to FXa inhibitor dosing; please note that these times may occur before or after dosing, depending on the identity of the inhibitor.
- Record concomitant medications and AEs.

6.4.3. Day 5

Procedures that Occur Throughout the Day

- Test stool samples submitted by subject for occult blood
- Record concomitant medications and AEs.

Prior to the Morning Dose of FXa Inhibitor

- Vital signs should be recorded within 90 minutes before FXa inhibitor administration.
- Obtain a 12-lead ECG and record the Investigator's reading.
- Collect local and central laboratory blood and urine samples at various times after dosing as delineated in Appendix B, Appendix B.
- Establish IV access into a peripheral vein at least 90 minutes prior to the FXa inhibitor dose (see Pharmacy Manual for further instructions)

Following the above, the FXa inhibitor should be administered. After the dose, the following should be performed (see Appendix B, Appendix B):

- Collect local and central laboratory and PK blood samples at various times after dosing as delineated in Appendix B, Appendix B.
- Administer second dose of FXa inhibitor as appropriate (See Appendix B, Appendix B).

Standardized meals are to be served at fixed times in relation to FXa inhibitor dosing; please note that these times may occur before or after dosing, depending on the identity of the inhibitor (see Section 5.5).

6.5. Andexanet/Placebo Dosing Day (Day 6)

Procedures that Occur Throughout the Day

- Test stool samples submitted by subject for occult blood (if produced).
- Record concomitant medications and AEs.

Prior to the Dose of FXa Inhibitor

- Perform physical examination.
- Vital signs should be recorded within 90 minutes before FXa inhibitor administration.
- Perform pulse oximetry (see Section 7.5.4).
    - Obtain 12-lead ECG (record electronically) and record Investigator's reading.
    - Collect local and central laboratory samples and urinalysis (see Appendix B, Appendix B).
    - Establish IV access into a peripheral vein at least 90 minutes prior to the andexanet dose (see Pharmacy Manual for further instructions).
    - Serve standardized meals at fixed times as appropriate.

Administer the (Final) Dose of FXa Inhibitor

Depending on the cohort, andexanet dosing (and all downstream assessments) will start at various times after the final dose of FXa inhibitor. For Cohorts 1, 3, 5, and 6, andexanet will be administered beginning 3 hours after the final anticoagulant dose. For Cohort 2, andexanet will be administered beginning 4 hours after the final dose of rivaroxaban. For Cohorts 4 and 7, andexanet will be administered starting 90 minutes after the last dose of edoxaban. For Cohorts 8, 9, and 10, andexanet will be given 8 hours after the last dose of FXa inhibitor.

After the (Final) Dose of FXa Inhibitor, Prior to the Start of Andexanet

- Obtain vital signs and pulse oximetry immediately prior to the start of andexanet.
- Collect local and central laboratory samples as delineated in Appendix B, Appendix B after administering the FXa inhibitor.

Administer Andexanet/Placebo Bolus

- Bolus is to start 3 hours after administering FXa inhibitor for Cohorts 1, 3, 5, and 6.
- Bolus is to start 4 hours after administering rivaroxaban for Cohort 2.
- Bolus is to start 1.5 hours after administering edoxaban in Cohorts 4 and 7.
- Bolus is to start 8 hours after administering FXa inhibitor for Cohorts 8 to 10.

During Andexanet/Placebo Bolus

- Obtain vital signs and pulse oximetry at 3 minutes and 10 minutes after the start of andexanet/placebo bolus.

After Andexanet/Placebo Bolus

- Start andexanet/placebo infusion immediately after andexanet bolus is completed.
- Obtain vital signs and pulse oximetry 2 and 5 minutes after the bolus is completed.
- Collect local and central laboratory samples 2 and 5 minutes after the bolus is completed.
- Obtain 12-lead ECG (record electronically) and record investigator's assessment 5 minutes after the bolus is completed.

Forty-Five Minutes into the Continuous Infusion

- Obtain vital signs and pulse oximetry.
- Collect local and central laboratory samples (see Appendix B, Appendix B).

Ninety Minutes into the Continuous Infusion

- Collect central laboratory samples (see Appendix B, Appendix B).

One Hundred Ten Minutes into the Continuous Infusion

- Collect central laboratory samples (see Appendix B, Appendix B).

Two Minutes Prior to the End of the Continuous Infusion

- Collect central laboratory samples (see Appendix B, Appendix B).

After the Continuous Infusion

- Obtain vital signs and pulse oximetry at 5 minutes after the end of the continuous infusion.
- Obtain 12-lead ECG (record electronically) 5 minutes after the end of the continuous infusion and record Investigator's assessment.
- Collect local and central laboratory samples at the following times after the end of the continuous infusion: 5, 30, 60, 90, 120, 150, 180, 210, 270, 330, 390, 450, 510, and 870 minutes (see Appendix B, Appendix B). For Cohorts 8-10, no laboratory samples should be drawn at the 870 minute time point.
- Perform clinical VTE screening 180 minutes (± 30 minutes) after the end of the continuous infusion.

6.6. Inpatient Post-Treatment Follow Up (Days 7–10)

6.6.1. Day 7

The following procedures should be performed approximately 24 hours after the last dose of the FXa inhibitor on Day 6:

- Perform physical exam and clinical VTE screening.
- Obtain vital signs.
- Obtain 12-lead ECG (record electronically) and record Investigator's assessment.
- Test stool samples submitted by subject for occult blood (if produced).
- Collect local and central laboratory samples and urinalysis (see Appendix B, Appendix B).
- Record concomitant medications and AEs.

6.6.2. Days 8 to 9

- Obtain vital signs.
- Test stool samples submitted by subject for occult blood (if produced).
- Collect local and central laboratory samples (see Appendix B, Appendix B).
- Record concomitant medications and AEs.

6.6.3. Day 10

- Perform physical examination and clinical VTE screen.
- Obtain vital signs.
- Obtain 12-lead ECG (record electronically) and record Investigator's assessment.
- Collect local and central laboratory samples and urinalysis (see Appendix B, Appendix B).
- Obtain serum pregnancy test in women.
- Test stool samples submitted by subject for occult blood (if produced).
- Record concomitant medications and AEs.
- Instruct subjects regarding the contraception requirements.
- Instruct subjects to contact the study site to report any AEs and new concomitant medications.
- Instruct subjects to return for the Day 20 outpatient visit.
- Discharge subjects from the study facility.

6.7. Outpatient Post-Treatment Follow Up (Days 11–36)

6.7.1. Day 20 (+3) Outpatient Visits

The following procedures should be performed at the Day 20 Outpatient Visit:

- Perform VTE screen.
- Record vital signs.
- Record AEs since last study visit.
- Record concomitant medication use since last study visit.
- Collect central laboratory samples (see Appendix B, Appendix B).
- Instruct subjects to contact the study site to report any AEs and new concomitant medications.
- Instruct subjects to return for the Day 36 outpatient visit.

6.7.2. Day 36 (+3) Outpatient Termination Visit

- Perform physical examination and VTE screen.
- Record vital signs.
- Obtain 12-lead ECG (record electronically) and record Investigator's assessment.
- Record AEs since last study visit.

- Record concomitant medication use since last study visit.
- Collect local and central laboratory samples and urinalysis (see Appendix B, Appendix B).
- Obtain a serum pregnancy test in women.
- Confirm negative drugs of abuse/breathalyzer screen.
- Discharge the patient from the study.

6.8. Unscheduled Visit

Additional clinical visits may be scheduled at the Investigators' discretion in order to follow or evaluate AEs. The reason for a given unscheduled visit will be recorded.

The following must be performed at an unscheduled visit:

- Record the reason for the unscheduled visit.
- Perform physical examination and VTE screen.
- Record vital signs.
- Record AEs since last study visit.
- Record concomitant medication use since last study visit.

The following may be performed at an unscheduled visit as deemed necessary by the Investigator:

- Collect local and/or central laboratory samples.
- Obtain 12-lead ECG and record Investigator's assessment.

6.9. Early Termination Visit

Should Early Termination be required, every effort should be made to have the subject return to the clinical site for an Early Termination Visit. The following procedures should be performed at the Early Termination Visit:

- Record the reason for early termination.
- Perform physical examination and VTE screening.
- Record vital signs.
- Obtain 12-lead ECG (record electronically) and record Investigator's assessment.
- Record AEs since last study visit.
- Record concomitant medication use since last study visit.

- Collect local laboratory samples for hematology and serum chemistry. Coagulation tests (PT, aPTT, and ACT) collected in Part 1 only.
- Collect central laboratory samples for anti-fXa activity, FXa inhibitor PK, thrombin generation, D-dimer, F1+2, anti-fX, -fXa, and –andexanet antibodies, and additional plasma sample if the Early Termination Visit occurs after andexanet has been administered.
- Perform any additional needed evaluation for AEs as determined by the Investigator.
- Collect serum pregnancy test.

6.10. Non-Contact Daily Exercise

While domiciled, subjects are encouraged to engage in regular, low level, non-contact exercise (e.g., walking laps within the research unit) to minimize the risk of thrombosis from inactivity. Because subjects will be anticoagulated some of this time, however, it is imperative no vigorous, contact sports are initiated as they may increase the risk of bleeding.

6.11. Early Discontinuation from Study

Subject discontinuation of study drug and/or the study will occur:

- If, in the opinion of the Investigator or Medical Monitor the subject cannot safely perform the procedures required by the protocol.
- If the subject has an AE that is unacceptable to the subject, Investigator or Medical Monitor.
- If there is a need for concomitant medication which makes the subject ineligible for further participation in the study.
- If the Investigator or Medical Monitor decides it is in the subject's best interest.
- If the subject decides to withdraw for whatever reason.
- If the subject is involved in a significant protocol deviation.

Subjects are free to withdraw from the study at any time for any reason, however, to the extent possible, all subjects should continue to participate in the study once they have enrolled, even if they discontinue study drug(s) early. Reasons for all withdrawals/discontinuation of study medications will be recorded and the Medical Monitor should be informed of all such cases as they occur. If a subject discontinues the study drug due to an AE, that AE must be evaluated for its reportability as an SAE. All SAEs must be reported to the Sponsor within 24 hours by the Investigator. The procedures described under the Study Termination/Day 40 Visit will be performed, if possible.

Normal study termination is defined as the completion of all procedures listed under Study Methods.

7.0 CLINICAL ASSESSMENTS

7.1. Blood Collection

Up to approximately 815 mL in Part 1 and 709 mL in Part 2 of blood will be drawn from each subject over the 6 to 10 week course of the study. Approximately 650 mL in Part 1 and 555 mL in Part 2 of blood (comparable to the amount of blood drawn over ~10 minutes during a single Red Cross blood donation—480 mL) will be drawn over the 10 day domiciled period of the study, and the remaining amount of blood will be drawn during Screening (~31 mL) or the ~5 week post-discharge follow up period (~134 mL in Part 1 and ~123 mL in Part 2).

7.2. Screening/Eligibility Assessments

7.2.1. Urine Drugs of Abuse Screen

The following panel will be obtained on Day -1 and the Termination Visit (Day 36 +3) to ensure study subjects are not using drugs of abuse: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol, and opiates.

7.2.2. Breathalyzer Ethanol Screen

To evaluate for the recent ingestion of ethanol, a breathalyzer test will be performed on Day -1 and the Termination Visit (Day 36 +3).

7.2.3. Blood Laboratory Testing

Blood will be obtained to measure several parameters for the purposes of screening and assessment of eligibility. All test samples will be analyzed by a laboratory at the discretion of the study center. Specifically, these will include the following:

- Screening for asymptomatic pro-thrombotic, hypercoagulable conditions by testing for Factor V Leiden, Protein S, Protein C, and Anti-Thrombin III at the Screening Visit.
- Hepatitis B surface antigen at the Screening Visit.
- Hepatitis C antibody at the Screening Visit.
- HIV-1 and HIV-2 antibodies at the Screening Visit.
- Blood will be obtained at Screening, Day -1, Day 10, and Termination Visit (Day 36 +3) from all female subjects to determine their pregnancy status (serum pregnancy test and/or FSH as appropriate).

7.3. Efficacy Assessments

7.3.1. Coagulation Assays

Blood will be obtained to determine the effects of andexanet on various components of the human coagulation system, as a marker of both safety and PD activity, at various time points throughout the study. Specifically, these will include the following:

Part 1

- Anti-fXa activity and thrombin generation will be measured using plasma samples collected at the site to assess the ability of observed andexanet blood levels to reverse the anticoagulant effect of apixaban, edoxaban, and rivaroxaban.
- PT, aPTT, and ACT, all of which will be measured/analyzed locally at the study site.
- FX, F1+2, TAT, D-dimer (fibrin degradation fragment), fibrinogen, TFPI [total and free antigen], TFPI activity), Russell's Viper Venom Time (RVVT), TAFI, tPA, b-TG, PF4, sTM, and PAP will be assessed in plasma samples collected at the site and shipped to an outside laboratory for analysis.

Part 2

- Anti-fXa activity and thrombin generation will be measured using plasma samples collected at the site to assess the ability of observed andexanet blood levels to reverse the anticoagulant effect of apixaban, edoxaban, and rivaroxaban.
- PT, aPTT, and ACT will be measured/analyzed locally at the study site at screening only.
- F1+2, TAT, D-dimer (fibrin degradation fragment), and TFPI activity will be assessed in plasma samples collected at the site and shipped to an outside laboratory for analysis.

7.4. Pharmacokinetic Assessments

Plasma samples will be obtained at selected time points and analyzed for the concentration of andexanet and the FXa inhibitors. Sample assays for drug concentrations will be performed using validated electrochemiluminescent (andexanet) or LCMS (apixaban, edoxaban, and rivaroxaban) methods. Unbound plasma concentrations for apixaban, edoxaban, and rivaroxaban will be determined by an equilibrium dialysis method followed by LCMS for quantitation. Details on the collection, processing, storage, and shipment of samples are contained in the Study Manual. Specific PK parameters to be evaluated are listed in Section 9.0.

7.5. Safety Assessments

Safety and tolerability will be determined by symptoms, signs, and laboratory test abnormalities. The Investigator will monitor the laboratory test findings. If any laboratory test is abnormal during the course of the study, it will be followed at the discretion of the Investigator. Abnormalities of laboratory tests may, in the opinion of the Investigator be considered clinically significant and, thus, constitute or be associated with an AE. In such cases, they must be reported on the Adverse Event Form.

In the event of an AE such as an allergic reaction, additional laboratory tests including the following should be considered for inclusion in the workup: hematology with differential, chemistry panel, cortisol level, Radioallergosorbent Test (RAST), tryptase, immunoglobulin levels (e.g., Immunoglobulin E). If possible, and necessary for interpreting such an AE, these labs may also be retroactively added to the baseline assessment to determine if the laboratory test changed in the context of the AE.

7.5.1. Vital Signs

Vital signs include temperature, respiratory rate, heart rate, and blood pressure. Additionally, height and weight will be measured at Screening. Whenever possible, vital signs will be obtained after at least 5 minutes in the sitting position or, when necessary, in a semi-recumbent position. If vital signs must be obtained in the supine position due to ongoing drug infusion, an attempt should be made to obtain peri-infusion vital signs (e.g., the vital sign time points preceding and following the infusion) in the sitting position as well.

7.5.2. Physical Examination

Scheduled physical exams must include at a minimum an examination of the head, ears, nose and throat, heart, lungs, abdomen, skin, extremities, and peripheral pulses, and a brief neurologic exam.

7.5.3. Clinical Venous Thromboembolism Assessment

In addition to regular assessment of all AEs, specific scoring systems designed to detect risk of thromboembolic disease will be systematically administered throughout the conduct of the study. These tools—the Wells score for DVT and PE, respectively - offer an additional mechanism and improved surveillance for evidence of thrombotic events. The scoring systems may be found in Appendix C.

7.5.4. Oxygen Saturation

Oxygen saturation will be monitored by pulse oximetry during andexanet administration. It is recommended, though not required, that oxygen saturations not be measured on an extremity undergoing an active intravenous infusion.

7.5.5. Electrocardiogram

At specified time points, a standard 12-lead resting ECG will be recorded electronically after at least 10 minutes in the supine position.

7.5.6. Fecal Occult Blood Testing

Stool fecal occult blood testing will be performed daily from Day -1 to Day 10, inclusive. Occult blood testing may be deferred if no stool is available on a given day. A potential subject is excluded during Screening if a stool sample is positive for occult blood during Screening or

Day -1. During the treatment period (i.e., Days 1–8), occult blood testing may be deferred if no stool is available on a given day.

7.5.7. Clinical Laboratory Blood Testing

Blood specimens for routine chemistry and hematology will be obtained at selected time points. The assays will be performed at a local laboratory:

- Hematology (hemoglobin, hematocrit, White Blood Cell [WBC], platelet count, Complete Blood Count [CBC] differential).
- Serum Chemistry (sodium, potassium, chloride, carbon dioxide [bicarbonate], glucose, Blood Urea Nitrogen [BUN], creatinine, Aspartate aminotransferase [AST], Alanine aminotransferase [ALT], Creatine Kinase [CK], lactate dehydrogenase, total protein, albumin, alkaline phosphatase, calcium, phosphorous, total and fractionated [indirect or direct] bilirubin, uric acid).

The results of tests run local to the study site will be stored in the study database.

7.5.8. Urine Studies

Urine will be obtained at selected time points for the following laboratory tests:

- Complete urinalysis (specific gravity, pH, glucose, protein, hemoglobin, and microscopic urinalysis).

The results of tests run at the study site will be stored in the study database.

7.5.9. Immunogenicity

Monitoring for antibodies to andexanet, human FX, and human FXa will be done at specific time points using validated electrochemiluminescent methods at a central laboratory. For any sample which is confirmed positive for antibodies to andexanet, the potential for neutralizing antibody activity will be assessed by measuring the functional activity of andexanet in plasma. This test will be performed at a central laboratory. Plasma samples at specific time points will be tested for potential neutralizing antibody activity against endogenous FX/FXa using a modified Bethesda assay. This test will be performed at a central laboratory.

8.0 ADVERSE EVENTS/SAFETY MONITORING

8.1. General Safety Considerations

While this type of study is typically designed as a 2-period crossover trial, a parallel group design is used in this case in order to minimize the risk of immunogenicity in healthy subjects. Furthermore, to monitor for immunogenicity, blood specimens will be serially evaluated at each outpatient follow-up visit (Days 20 and 36) for antibodies against andexanet, FX, and FXa. Samples that are positive for antibodies to andexanet will be further assayed for the ability to neutralize the activity of andexanet. Plasma samples at specific time points will be tested for potential neutralizing antibody activity against endogenous FX/FXa using a modified Bethesda assay.

Subjects will be monitored while domiciled in the clinical site for the entire period that they are anticoagulated with FXa inhibitors and for 4 days after administration of andexanet. Although there have been no thromboembolic events in any healthy subjects dosed with andexanet thus far, some prothrombotic markers (D-dimer, F1+2, and TAT) transiently increase following andexanet infusion, generally resolving within 4 days after andexanet treatment. This increase is diminished when andexanet is coadministered with an FXa inhibitor, as will be the case in the present study. D-dimer, F1+2, and TAT will be obtained and reviewed in the present study. Furthermore, a clinical assessment of venous thromboembolism risk (via Wells Scoring) will be performed at multiple time points during the study.

Prior and ongoing clinical studies have identified infusion reactions of mild or moderate intensity as the most common adverse event related to administration of andexanet. Although no severe or serious infusion reactions have occurred to date in healthy subjects receiving andexanet, subjects in this study will receive andexanet in an inpatient, monitored setting under medical supervision and immediate access to resuscitative measures. Notably, infusion reactions observed in prior and ongoing studies have had their onset during the infusion itself. Therefore, in addition to vital signs, oxygen saturation will be monitored during the infusion.

To monitor for occult bleeding, stool occult blood testing will be performed daily on stool samples produced throughout the period subjects are domiciled. The relatively short t½ of each FXa inhibitor predicts a loss of anticoagulant effects within 24 hours of the end of treatment. Following discharge from the clinical site, subjects will return for follow-up on Days 20 and 36 for safety follow-up.

Finally, safety data will be reviewed by the Sponsor on an ongoing basis.

8.2. Adverse Event Definition

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product, which may or may not have a causal relationship with the treatment. An AE can be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug-related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

8.3. Serious Adverse Event Definition

An SAE is any AE, occurring at any dose and regardless of causality that:

- Results in death.
- Is life-threatening. Life-threatening means that in the opinion of the Investigator or Study Sponsor, the patient/subject was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the subject was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Clarification should be made between the terms "serious" and "severe" since they **are not** synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe pain); the event itself, however, may be of relatively minor medical significance. This is **not** the same as "serious," which is based on the strict regulatory definitions listed above. A severe adverse event does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE if the event does not meet the serious criteria. On the other hand, a stroke

resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted serious criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.4. Suspected Unexpected Serious Adverse Reactions (SUSARs)

SUSARs are serious AEs that are both unexpected (i.e., the nature or severity is not expected from the information provided in the Investigator's Brochure) and assessed by the Investigator or the Sponsor's Medical Monitor to have a reasonable possibility of a causal relationship to the investigational medical product. The study Sponsor is required to submit to the FDA any SUSAR as an IND Safety Report within an expedited timeline; thus it is important for the Investigator to submit all SAEs promptly to the Sponsor for determination of expedited reporting to FDA.

8.5. Adverse Events of Special Interest

The following are Adverse Events of Special Interest (AESIs) and should be reported as adverse events (or as SAEs, if appropriate) within 24 hours after which the Investigator is made aware of them, as described in Section 8.6:

- VTE of any severity
- Severe infusion reaction
- Antibodies to factor X or factor Xa

8.6. Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient/subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the appropriate forms in the electronic Case Report Form (e-CRF). Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded on the appropriate forms in the e-CRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. For example, the combination of general malaise, mild fever, headache and rhinitis should be described as "common cold" symptoms rather than for each symptom to be listed separately.

All SAEs and AESIs that occur during the course of the study, as defined by the protocol, must be reported by the Investigator to Portola Product Safety by faxing the SAE Form within 24 hours from the point in time when the Investigator becomes aware of the SAE or AESI. In addition, all SAEs including all deaths, which occur until the termination visit must be reported to Portola Product Safety within 24 hours. All SAEs, AESIs, and deaths must be reported, whether or not considered causally related to the study drug. The SAE form will be provided to each clinical study site. The information collected will include at minimum the following:

subject number, the criteria met for the AE being serious, the event term, a narrative description of the event and an assessment by the Investigator as to the severity/intensity of the event and relatedness to study drug. Follow-up information on the SAE or AESI should be sent promptly by the Investigator to Portola when any additional relevant information about the SAE becomes known to the Investigator, or as requested by Portola.

SAE Reporting Contact Information

Portola Pharmacovigilance Vendor:

C3i Solutions (formerly TELERx)

Email: **PortolaSafety-SAE-AE@Telerx.com**

If the question needs further evaluation, please contact:

Portola Pharmacovigilance at:

PV@portola.com

If a serious AE meets the definition of a SUSAR, Portola will notify the appropriate regulatory agency (or agencies) and all participating Investigators on an expedited basis. Additionally, Portola will promptly notify the Investigator if any additional safety or toxicology information becomes available during the study. It is the responsibility of the Investigator to promptly notify the IRB/IEC of all unexpected serious adverse drug reactions involving risk to human subjects. An unexpected event is one that is not listed by nature or severity in the Investigator's Brochure.

Planned hospital admissions or surgical procedures for an illness or disease which existed before the subject was enrolled in the trial or before study drug was given are not to be considered AEs unless they occur at a time other than the planned date for a reason such as a worsening of the underlying disease/illness/symptoms.

For both serious and non-serious AEs, the Investigator must determine both the severity of the event and the relationship of the event to study drug.

The severity should be defined according to the following criteria:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with normal daily activities
Severe	Inability to perform normal daily activities
Life Threatening	Immediate risk of death from the reaction as it occurred
Fatal	Event resulted in death

The causal association of AEs to study drug administration (the factor Xa inhibitor, andexanet, or matching placebo) should be determined as follows:

Unrelated/Unlikely The current state of knowledge indicates that a relationship is not reasonable or is unlikely. Other plausible explanations exist for the AE.

Possible/Probable There is a reasonable possibility that the AE may have been caused by the drug, either because of temporal relationship to study drug administration, plausibility based on study drug pharmacology and PKs, and/or lack of evidence suggesting other possible causes of the event (e.g., intercurrent illness, concomitant medication).

8.7. Procedures for Reporting SUSARs

All SAEs, regardless of relationship to study drug, should be promptly reported by the Investigator to the Sponsor using the SAE reporting email.

A SUSAR which is fatal or life threatening must be reported to the FDA and ethics committee immediately (within 7 days) after the Sponsor became aware of the event. A follow up report with as much additional information as is available will be filed within 8 additional calendar days.

A SUSAR which is not fatal or life-threatening, but meets other criteria of seriousness, must be reported by the Sponsor to the FDA and Ethics Committee as soon as possible (no later than 15 calendar days) after the Sponsor becomes aware of the event.

8.8. Monitoring of Adverse Events and Period of Observation

Adverse events, both serious and non-serious, occurring between signing informed consent and up to and including the Termination Visit will be recorded on the e-CRFs. All AEs and SAEs should be monitored until they are resolved, reach a level of stability and are not expected to improve further, or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness.

Any AE or SAE that occurs with an onset date after completion of the study, and that the Investigator considers to be related to study medication, must be reported to Portola.

8.9. Procedures for Reporting Pregnancy Exposure and Birth Events

If a woman who is a study subject becomes pregnant or a woman partner of a male study subject becomes pregnant from a male study subject (between study drug administration and up to 16 weeks after the termination visit), the Investigator should be informed immediately. The Sponsor must in turn also be notified by the Investigator immediately by completing a Pregnancy Form and faxing it to Portola Product Safety (see Section 8.5). In the event a female partner of a male subject is pregnant or suspects she is pregnant by the male subject, the male subject will be advised by the study Investigator to have his female pregnant partner inform her treating

physician immediately. The pregnancy must be followed up through delivery or other fetal outcome. For any abnormal fetal outcome, including congenital anomaly or birth defect, spontaneous or therapeutic abortion, still birth, pre-mature birth, or other outcome other than live normal birth, the Investigator should promptly report to the Sponsor the abnormal fetal outcome on an SAE form.

9.0 PHARMACOKINETIC ANALYSES

The following noncompartmental PK parameters for plasma andexanet will be calculated for all subjects:

- Plasma $t_{½}$, determined by linear regression of the log concentration on the distribution and terminal portion of the plasma concentration–time curve. Distribution half-life is calculated as ln(2)/(- α), where α is the slope of the distribution portion of the log concentration–time curve. Terminal half-life is calculated as ln(2)/(- β), where β is the slope of the terminal portion of the log concentration–time curve;
- Time to maximum observed plasma concentration (T_{max})
- C_{max}
- Area under the plasma concentration–time curve from 0 to last measurable concentration ($AUC_{(0–last)}$) computed using the linear trapezoidal rule
- Total area under the plasma concentration–time curve from time 0 to infinity ($AUC_{(0-\infty)}$), computed as:

  $$AUC_{(0-\infty)} = AUC_{(0–last)} + C_{plast} /(- \beta)$$

  where $AUC_{(0–last)}$ is the AUC from time 0 to the time point of the last measurable concentration above the quantitation limit; C_{plast} is the last measurable concentration above the quantitation limit; and β is defined as above
- Clearance (CL)
- Volume of distribution at steady state (V_{ss})
- The terminal or elimination rate constant (λ_z)

The following non-compartmental parameter estimates from Cohorts 1 and 5 will be calculated to evaluate the PK of andexanet in Japanese versus Caucasian subjects:

- C_{max}
- $AUC_{(0-\infty)}$
- $AUC_{(0–last)}$
- $t_{½}$
- CL
- V_{ss}
- λ_z

PK parameters for apixaban, rivaroxaban, edoxaban, and the edoxaban metabolite D21-2393 will be assessed at Day 1 (pre-dose only), multiple time points on Day 5 through Day 8 and once on Day 9 and Day 10. The following PK parameters will be calculated for apixaban, edoxaban, and rivaroxaban based on total plasma concentrations:

- $t_{½}$
- T_{max}
- C_{max}
- C_{bolus} (end of the bolus plus 2 minutes)
- $AUC_{(0–last)}$
- Area under the plasma concentration–time curve between dosing interval ($AUC_{(0-\tau)}$)
- Clearance (CL/F)
- λ_z

10.0 STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

10.1. Study Objectives and Study Design

The study objectives and study design are described in Section 2.0 and Section 3.1, respectively.

10.2. General Considerations

All statistical summaries will be performed using SAS Version 9.2 (SAS Institute, Inc., Cary, NC, USA) or higher. Additional software may be used for the production of graphics.

A Statistical Analysis Plan (SAP) will be created for this study, with appropriate details and definitions of all analyses. For selected interim analyses, the SAP will be archived prior to any interim database lock associated with that respective analysis.

All hypothesis tests will be two-sided and performed at the 0.05 significance level.

10.3. Randomization

Depending on cohort assignment, subjects will be randomized in a 2:1 ratio to receive andexanet or placebo, respectively. The detailed randomization process is described in Section 3.2.1. Subjects will be randomized on Day 1, once it is ascertained that they meet all of the inclusion/exclusion criteria. At this time the unblinded research pharmacist or designee will obtain the subject's treatment assignment. The randomization code and starting seed will be generated by a CRO and maintained by a CRO. The code will not be provided to the Sponsor, the site (aside from the unblinded research pharmacist or designee), or subjects until the database has been locked, except as required for non-study personnel in the regulatory reporting of SAEs.

10.4. Analysis Populations

10.4.1. Efficacy Analysis Population

The efficacy analysis population will include all randomized subjects who took any amount of study medication (andexanet or placebo) during the double-blind treatment period. For the efficacy analysis, subjects will be presented in the treatment group to which they were randomized. Subjects will be included in the efficacy analysis on change or percent change from baseline if they have a baseline and at least one measurement post-baseline for the time point under consideration.

10.4.2. Safety Analysis Population

The safety analysis population will consist of all subjects randomized and treated with study medication (andexanet or placebo). All safety analyses will be performed by actual treatment received. Subjects who received one or more doses of FXa inhibitor but discontinued prior to receiving study drug will be listed separately.

10.4.3. PK Analysis Population

The PK analysis populations will consist of all subjects who have received the requisite treatments and have sufficient data to calculate each PK parameter. Any windows for timing of measurements, etc. will be specified in the SAP.

10.5. Endpoints

10.5.1. Efficacy Endpoints

10.5.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the difference in percent change in the anti-fXa activity from baseline to the nadir level at the end of the infusion between andexanet- and placebo-treated subjects. Nadir is defined as the smallest value for anti-fXa activity between the 110-minute time point (10 minutes prior to the end of the continuous andexanet infusion) and the 5-minute time point after the end of the continuous infusion (inclusive). The primary analysis will be performed on all individual cohorts separately.

10.5.1.2. Secondary Efficacy Endpoint

The secondary efficacy endpoints include the following:

- The percent change from baseline in anti-fXa activity at its nadir, where nadir is defined as the smallest value for anti-fXa activity at the +2 minute or +5 minute time point after the completion of the andexanet bolus.
- The change from baseline in free FXa inhibitor concentration (ng/mL) at its nadir, where nadir is defined as the smallest value for free FXa inhibitors at the +2 minute or +5 minute time point after the completion of the andexanet bolus.
- The change from baseline in free FXa inhibitor concentration (ng/mL) at its nadir, where nadir is defined as the smallest value for free FXa inhibitors between the 110-minute time point (10 minutes prior to the end of the continuous infusion) and the 5-minute time point after the end of the continuous infusion (inclusive).
- The change in thrombin generation from baseline to its peak, where peak is defined as the largest value for thrombin generation between the +2 minute time point and the +5 minute time point after the end of the andexanet bolus (inclusive).
- The occurrence of thrombin generation above the lower limit of the normal range at its peak, between the +2 minute time point and the +5 minute time point after the end of the andexanet bolus (inclusive).
- The change in thrombin generation from baseline to its peak, where peak is defined as the largest value for thrombin generation between the 110-minute time point (10 minutes prior to the end of the continuous infusion) and the 5-minute time point after the end of the continuous infusion (inclusive).

- The occurrence of thrombin generation above the lower limit of the normal range at its peak, where peak is defined as the largest value for thrombin generation between the 110-minute time point (10 minutes prior to the end of the continuous infusion) and the 5-minute time point after the end of the continuous infusion (inclusive) and assess the thrombin generation during 24 hours after administration of FXa inhibitors.

10.5.1.3. Exploratory Efficacy Endpoints

For Parts 1 and 2 of the study, TFPI activity, a marker of endogenous anticoagulation, will be evaluated for the purpose of monitoring the potential procoagulant activity of andexanet (due to andexanet-TFPI interaction).

For Part 1 of the study the following additional markers will also be examined:

- PT
- aPTT
- ACT
- FX
- fibrinogen
- tPA
- PAP
- TAFI
- b-TG
- PF4
- sTM
- TFPI (total and free antigen)

10.5.2. Safety Endpoints

10.5.2.1. Non-Laboratory-Based Endpoints

Safety will be evaluated by assessment of adverse events, venous thromboembolic events, physical exam findings, vital signs, oxygen saturation, fecal occult blood testing, and 12-lead ECGs.

10.5.2.2. Laboratory-Based Endpoints

Routine clinical laboratory parameters to be evaluated include hematology, chemistry, urinalyses, and coagulation markers (D-dimer, F1+2, and TAT).

Immunogenicity will be evaluated by measurement of antibodies to andexanet, FX, and FXa. In addition, neutralizing antibodies for any confirmed antibody response will be measured for andexanet. Furthermore, potential neutralizing antibody activity against FX/FXa will be assessed by a clotting based modified Bethesda assay.

In Part 1 of the study, Russell's Viper Venom Time (RVVT) was included as an additional assessment.

10.5.3. PK Endpoints

PK endpoints are summarized in Section 9.0.

10.6. Statistical Analyses

10.6.1. Baseline and Demographics

Baseline and demographic characteristics will be summarized for the safety and efficacy populations of each part of the study. Data will be summarized overall and by treatment using descriptive statistics such as frequencies, means, medians, standard deviations, minimums, and maximums. No inferential statistical analyses of these data are planned.

10.6.2. Efficacy Analysis

All efficacy analyses will be performed by treatment assigned at randomization.

10.6.2.1. Primary Efficacy Analysis

The primary analysis will be performed to compare the difference in the primary endpoint between andexanet- and placebo-treated subjects by cohort. The analysis will be performed in all cohorts. The comparison will be conducted using a two sample exact Wilcoxon rank sum test. All hypothesis tests will be 2-sided and performed at the 0.05 significance level. No adjustment for multiplicity is necessary since each cohort is considered as an independent population.

10.6.2.2. Secondary Efficacy Analyses

No formal statistical hypothesis testing will be performed for the secondary endpoints but point estimates and two-sided 95% confidence intervals will be produced to assess the treatment effects with respect to the secondary endpoints.

10.6.2.3. Exploratory Efficacy Analyses

Plots of the values and change from baseline over time for TFPI activity will be evaluated by treatment in placebo-controlled cohorts from all parts of the study. For Part 1 of the study, the additional exploratory endpoints of TFPI (total and free antigen), PT, aPTT, ACT, FX, fibrinogen, tPA, PAP, TAFI, b-TG, P44 and sTM were also collected and will be presented. If data permit, the comparison between treatment groups may be made at an appropriate time.

10.6.2.4. Handling of Missing Data

If there are insufficient post-baseline data to evaluate the endpoint, imputation will be carried out. Detailed imputation methods will be defined in the Statistical Analysis Plan. If a subject

discontinues prematurely from the study or otherwise has missing data, the Sponsor may elect to enroll up to 3 additional subjects per cohort.

10.6.3. Subgroup Analysis

Due to the size of this study, no inferential subgroup analyses are planned.

10.6.4. Safety Analysis

10.6.4.1. Extent of Exposure

Dosing information for each drug and each subject will be listed. Discontinuation of dosing will be summarized by treatment received. The primary reason for study drug discontinuation will also be summarized by treatment received.

10.6.4.2. Analysis of Adverse Events

Treatment-Emergent Adverse Events (TEAEs) will be summarized by treatment, system organ class, and preferred term defined by the Medical Dictionary for Regulatory Activities (MedDRA, version 16.1 or later).

The number of events, the number of subjects, and the percentage of subjects who experienced at least one TEAE will be presented. TEAEs that are considered by the investigator to be related to study medication, TEAEs that lead to early withdrawals, and serious TEAEs will be summarized in the same manner.

The treatment groups will be compared in regards to safety endpoints descriptively. No inferential comparison will be conducted.

10.6.4.3. Concomitant Medications

Concomitant medications will be coded using the September 2013 version of WHO-Drug.

10.6.4.4. Analysis of Laboratory Parameters

Clinical laboratory parameters including hematology, chemistry, urinalyses, and coagulation markers (D-dimer, TAT and F1+2, PT, aPTT, and ACT) will be summarized by treatment group and by time point for the cohorts that the data was collected.

Baseline values, the values at each subsequent visit, and changes from baseline will be summarized for each of the quantitative laboratory assessments by treatment.

Shift tables of chemistry, hematology, and urinalysis results will be used to summarize changes from baseline to study termination (or early termination).

The number and percentage of chemistry, hematology, and urinalysis values outside of normal ranges and/or with Potential Clinical Importance will be summarized by visit and treatment.

The presence of antibodies (anti-andexanet, anti-fX, anti-fXa, and/or neutralizing antibodies) will be listed.

10.6.4.5. Analysis of Other Safety Parameters

Vital signs, oxygen saturation, results from clinical VTE assessments, and ECG intervals will be summarized using actual values and change from baseline at pre-specified time points for each treatment group. Descriptive statistics, including threshold-based outlier analyses will be presented. ECG abnormalities will be listed.

10.6.5. PK Analysis

PK parameters defined in Section 10.5.3 will be calculated by subject and summarized by cohort. Only subjects with sufficient data to calculate each PK parameter will be included in the summary of each PK endpoint.

10.6.6. Interim Analysis

Following the completion of Part 1, an unblinded analysis of data from Part 1 may be performed to inform dosing in Part 2. Data from Part 2 will remain blinded following the analysis of Part 1 data. The parameters to be reviewed will be determined at the time of the analysis. Additional unblinded interim analyses may be performed on selected cohorts following their completion (and prior to study completion) to enable and support regulatory submissions or the Sponsor's decision making. The detailed unblinding procedures for the interim analysis will be separately documented in an Unblinding Plan.

10.7. Sample Size Considerations

10.7.1. Part 1

10.7.1.1. Apixaban (Cohorts 1 and 5)

The mean (SD) of the primary endpoint in Study 14-503 Part 2 which assessed the reversal of apixaban 5 mg BID anticoagulation with andexanet administered as an IV bolus followed by a 2-hour infusion were -92.3% (SD = 2.8%) and -32.7% (SD = 5.6%) for andexanet and placebo arms, respectively. Based on these results, the percent changes from baseline in anti-fXa activity in this study are assumed to be -90% (SD = 5%) and -35% (SD = 10%) for andexanet and placebo arms, respectively. The standard deviations in both arms are assumed larger than the observed values in the previous study to provide adequate power for the comparison. Under these assumptions, a total number of 9 subjects (6 active and 3 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test.

10.7.1.2. Rivaroxaban (Cohort 2)

The mean (SD) of the primary endpoint in Study 14-504 Part 2 which assessed the reversal of rivaroxaban 20 mg QD anticoagulation with andexanet administered as an IV bolus followed by a 2-hour infusion were -96.7% (SD = 1.8%) and -44.8% (SD = 11.7%) for andexanet and placebo arms, respectively. Based on these results, the percent changes from baseline in anti-fXa activity are assumed to be -90% (SD = 5%) and -45% (SD = 15%) for andexanet and placebo arms, respectively. Under these assumptions, a total number of 9 subjects (6 active and 3 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test.

10.7.1.3. Edoxaban (Cohort 3; andexanet dosing at 3 hours post-edoxaban)

In Cohort 2 of Study 12-502 Module 4, which assessed the reversal of edoxaban anticoagulation with andexanet, the mean (SD) of the percent change from baseline anti-fXa activity at the end of infusion was -70.28% (SD = 5.64%) for the andexanet arm. In Cohort 1 and Cohort 2 of the same study, the mean (SD) of the percent change from baseline at 2 hours after the end of bolus was -40.31% (SD = 12.25%) for placebo. Based on these results, the percent changes from baseline in anti-fXa activity for andexanet and placebo are assumed as -70% (SD = 6%) and -40% (SD = 15%), respectively. Under these assumptions, a total number of 12 subjects (8 active and 4 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test.

10.7.1.4. Edoxaban (Cohort 4; andexanet dosing at 90 minutes post-edoxaban)

There are no actual data of andexanet administration at 90 minutes after edoxaban dosing. Based on the result predicted by the PK-PD model developed using the data of Study 12-502, the percent changes from baseline in anti-fXa activity for andexanet and placebo are assumed as -70% (SD = 15%) and -30% (SD = 15%), respectively. Under these assumptions, a total number of 12 subjects (8 active and 4 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test.

10.7.2. Part 2

10.7.2.1. Apixaban 10 mg BID (Cohort 6: andexanet dosing at 3 hours post apixaban)

A total number of 9 subjects (6 active and 3 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test. The underlying assumptions are supported by data from Cohort 8 of the 16-512 study, which the mean (SD) of %change from baseline in anti-fXa activity (%CHB in anti-fXa activity) at nadir around EOI were -97% (SD = 0.8%) and –36% (SD = 3.3%) for andexanet and placebo arms, respectively. In the power calculation, -95% (SD = 10%) and -40% (SD = 10%) are assumed.

10.7.2.2. Edoxaban 30 mg QD (Cohort 7: andexanet dosing at 90 min post edoxaban)

A total number of 12 subjects (8 active and 4 placebo) will provide approximately 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test. Given the dose proportionality, the underlying assumptions are supported by data from Cohort 4 of the 16-508 study, which the mean (SD) of %CHB in anti-fXa activity at nadir around EOI were -71% (SD = 13.6%) and –34% (SD = 12.8%) for andexanet and placebo arms, respectively. In the power calculation, -70% (SD = 15%) and -35% (SD = 15%) are assumed.

10.7.2.3. Apixaban 10 mg BID (Cohort 8: andexanet dosing at 8 hours post apixaban)

A total number of 9 subjects (6 active and 3 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test. For placebo arm, the underlying assumptions are supported by data from Cohort 8 of the 16-512 study, which the mean (SD) of %CHB in anti-fXa activity at 3.5 hours after EOI was -51% (SD = 9.5%). For andexanet arm, the mean of %CHB in anti-fXa activity predicted by the PK-PD model that is 91.6% was used as reference because there are no actual data. In the power calculation,
-90% (SD = 10%) and -50% (SD = 10%) are assumed.

10.7.2.4. Rivaroxaban 15 mg BID (Cohort 9: andexanet dosing at 8 hours post rivaroxaban)

A total number of 15 subjects (10 active and 5 placebo) will provide approximately 87% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test. For placebo arm, the underlying assumptions are supported by data from Cohort 2 of the 16-508 study, which the mean (SD) of %CHB in anti-fXa activity at 1.5 hours after EOI was -56% (SD = 12.1%). For andexanet arm, the mean of %CHB in anti-fXa activity predicted by the PK-PD model that is 86.5% was used as reference because there are no actual data. In the power calculation, -85% (SD = 15%) and -55% (SD = 15%) are assumed.

10.7.2.5. Edoxaban 60 mg QD (Cohort 10: andexanet dosing at 8 hours post edoxaban)

A total number of 12 subjects (8 active and 4 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test. The underlying assumptions are supported by data from Cohort 11 of the 16-512 study, which the mean (SD) of %CHB in anti-fXa activity at nadir around EOI were -64% (SD = 9.0%) and –39% (SD = 6.0%) for andexanet and placebo arms, respectively. In the power calculation, -65% (SD = 10%) and -40% (SD = 10%) are assumed.

10.8. Institutional Review Board or Ethics Committee

The protocol and informed consent for this study must be reviewed and approved by an appropriate IRB or EC before subjects are enrolled in the study. It is the responsibility of the Investigator to assure that the study is conducted in accordance with current country and Local Regulations, International Conference on Harmonisation (ICH) GCP, and the Declaration of Helsinki. A letter documenting the approval which specifically identifies the protocol by number and title, as well as the Investigator must be received by the Sponsor prior to initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

After the completion or termination of the study, the Investigator will submit a report to the IRB or Ethics Committee and to the Sponsor.

10.9. Informed Consent

Each subject must be provided with oral and written information describing the nature and duration of the study, and sign a written informed consent before study entry. No subject is to be treated until an informed consent written in a language in which the subject is fluent has been obtained. The signed and dated informed consent will be retained with the study records. Each subject will also be given a copy of their signed informed consent.

10.10. Data Reporting and Case Report Forms

Data for each subject will be entered into the e-CRF and verified by the Investigator. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported on the subject's e-CRF. Source documentation supporting the e-CRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject's clinical status.

The Investigator or designated representative should complete the e-CRF as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment or any other study procedure. Any outstanding entries must be completed immediately after the final examination. CRF data will be processed in a US 21 CFR Part 11-compliant system.

10.11. Retention of Data

United States Federal regulations require that a copy of records (e.g., laboratory data slips, source documents, test article disbursement records, etc.), which support case records of this study must be retained in the files of the responsible Investigator for a minimum of two years following notification by the Sponsor that the FDA has approved a marketing application for the drug and indication being investigated, or the investigation has been terminated.

10.12. Deviation from the Protocol

The Investigator will not deviate from the protocol without first obtaining approval from the Sponsor and the IRB or Ethics Committee. In medical emergencies, the Investigator will use medical judgment and will remove the subject from immediate hazard, then notify the Sponsor's Medical Monitor and the IRB or Ethics Committee immediately regarding the type of emergency and course of action taken. Any action in this regard will be recorded on the appropriate CRF. Any other changes or deviations in the protocol will be made as an amendment to the protocol and must be approved by the Sponsor and the IRB or Ethics Committee and before they are implemented. The Sponsor will not assume any responsibility or liability for any unapproved deviation or change.

10.13. Study Monitoring

The Investigator will allow representatives of the Sponsor to periodically audit, at mutually convenient times before, during and after the study has been completed, all CRFs and relevant portions of office, clinical and laboratory records for each subject. The monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of CRFs, assure that all protocol requirements, applicable regulations and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

10.14. Drug Accountability

The Investigator must maintain accurate records of the amounts and dates study drugs were received from the Sponsor and dispensed to the subjects including the lot numbers, volume and concentration of stock suspension prepared and remaining stock suspension volume after dose preparation. All drug supplies must be accounted for at the termination of the study and a written explanation provided for any discrepancies. All partially used or unused drug supplies will be destroyed at the site in accordance with approved written procedures or returned to the Sponsor after written authorization is obtained from the Sponsor. The Investigator will maintain a record of the amount and dates when unused supplies were either destroyed or returned to the Sponsor. All records will be retained as noted in Section 10.11.

11.0 DISCLOSURE OF DATA

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Subject confidentiality will be further assured by utilizing subject identification code numbers to correspond to treatment data in the computer files. The study personnel, employees of the regulatory agencies, including the US FDA and the study sponsor, Portola Pharmaceuticals, Inc., and its agents will need to review subject medical records in order to accurately record information for this study. If results of this study are reported in medical journals or at meetings, the subject's identity will remain confidential.

12.0 REFERENCES

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13.0 APPENDICES

APPENDIX A. STUDY EVENTS FLOW CHART (PART 1)

Visit:	SCREENING [1]	ADMISSION	INPT	INPT	INPT	INPT
Day:	**≤ -45**	**-1**	**1**	**2**	**3**	**4**
Hour			0	0	0	0
Informed Consent	X					
Review/Complete I/E	X	X				
Medical History	X					
Medication History	X					
Physical Examination		X				
Vital Signs (sitting)	X	X	X	X	X	X
12-lead ECG	X					
Local Lab: Serum Chemistry	X					
Local Lab: Hematology	X	X				
Local Lab: Urinalysis	X					
Local Lab: Serum Pregnancy	X	X				
Local Lab: FSH	X					
Local Lab: Urine (drugs of abuse)		X				
Local Lab: Breathalyzer (Ethanol screen)		X				
Local Lab: Hep B & C, HIV I & II	X					
Local Lab: Factor V Leiden, Protein S&C, Anti-thrombin III	X					
Stool (occult blood) (if produced)	X	X	X	X	X	X
Randomization			X			
Administer Anticoagulant [2, 3]			X	X	X	X
Central Lab: Anticoagulant PK (blood)			X [4]			
Local Lab: PT, aPTT, ACT	X	X				
Central Lab: Thrombin generation			X [4]			
Central Lab: Anti-fXa activity			X [4]			
Central Lab: F1+2, TAT, D-dimer, total TFPI, TFPI activity			X [4]	X [5]	X [5]	X [5]
Central Lab: tPA, PAP, TAFI, free TFPI, b-TG, PF4, sTM			X [4]			
Central Lab: Fibrinogen, AT-III, FX			X [4]			
Central Lab: RVVT			X [4]			
Central Lab: Anti-fX, Anti-fXa, Anti-andexanet Antibodies (Neutralizing Antibodies as appropriate)			X [4]			
VTE Screening	X	X				
Concomitant Medication		X----------				----------X
Adverse Events		X----------				----------X

[1] Screening activities may be done on more than one day.

[2] qAM for edoxaban; q12h for apixaban and rivaroxaban; Window for dosing is ± 3 minutes.

[3] Last dose for all anticoagulants = Hour 0 (zero) on Day 6.

[4] To be completed after randomization but prior to administering 1st dose of anticoagulant (Day 1) or andexanet.

[5] To be completed within 5 minutes prior to anticoagulant administration.

Visit:	**INPT**										
Day:	**5**										
Hour:	**PRE**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**12**
Physical Examination											
Vital Signs	X										
12-lead ECG	X										
Local Lab: Serum Chemistry	X										
Local Lab: Hematology	X										
Local Lab: Urinalysis	X										
Stool (occult blood)	X										
Administer Anticoagulant [1, 2]		X [2]									X [2]
Central Lab: Anticoagulant PK (blood)	X		X	X	X	X	X	X	X	X	X
Local Lab: PT, aPTT, ACT	X		X [3]								
Central Lab: Anti-fXa Activity	X		X [3]								
Central Lab: Thrombin Generation	X		X [3]								
Central Lab: F1+2, TAT, D-dimer, Total TFPI, TFPI Activity	X		X [3]								
Central Lab: tPA, PAP, TAFI, Free TFPI, β-TG, PF4, sTM	X		X [3]								
Central Lab: Fibrinogen, AT-III, FX	X		X [3]								
Concomitant Medication	X……X										
Adverse Events	X……X										

[1] qAM for edoxaban; q12h for apixaban and rivaroxaban. Window for dosing is ± 3 minutes.

[2] Last dose for all anticoagulants = Hour 0 (zero) on Day 6.

[3] These laboratory measurements should be performed 24 hours prior to the end of the andexanet/placebo continuous infusion on Day 6. For Cohorts 1, 3, 5, and 6, collection should be 3 hours after FXa inhibitor dosing. For Cohort 2, collection should be 4 hours after the FXa inhibitor dose. For Cohorts 4 and 7, collection should be 90 minutes after the FXa inhibitor dose. For Cohorts 8, 9, and 10, collection should be 8 hours after the FXa inhibitor dose.

Visit:	**INPT**																								
Day:	**6**																								
	Hours Post Anticoagulant Dose					**End of Bolus**		**Minutes after the Start of Andexanet Infusion**				**Hours Post Completion of Andexanet Infusion**													
Hour for Cohorts 1, 3, 5, 6:	**PRE**	**0**	**1**	**2**	**3**																				
Hour for Cohort 2:	**PRE**	**0**	**1**	**2**	**4**	**End Bolus (+2 min)**	**End Bolus (+5 min)**	**45 min**	**90 min**	**110 min**	**End Infu-sion (-2 min)**	**5 min**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4.5**	**5.5**	**6.5**	**7.5**	**8.5**	**14.5**
Hour for Cohorts 4, 7:	**PRE**	**0**	**1**		**1.5**																				
Hours for Cohorts 8-10:	**PRE**	**0**	**1**	**2**	**8**																				
Physical Examination	X																								
Vital Signs	X				X [4]	X	X	X				X													
Pulse Oximetry	X				X [4]	X	X	X				X													
12-lead ECG	X						X					X													
Local Lab: Serum Chemistry	X																								X
Local Lab: Hematology	X																								X
Local Lab: Urinalysis	X																								X
Stool (occult blood)						X																			
Administer Anticoagulant [1, 2]		X [2]																							
Administer Andexanet					X [3]	X……..…….....X																			
Central Lab: Anticoagulant PK (blood)	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X		X	X
Central Lab: Andexanet PK (blood)					X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local Lab: PT, aPTT, ACT	X				X	X		X				X	X		X		X		X			X		X	
Central Lab: Anti-fXa Activity	X				X	X	X	X	X	X	X	X	X	X	X		X		X		X	X		X	X

Visit	**INPT**																								
Day	**6**																								
	Hours Post Anticoagulant Dose					**End of Bolus**		**Minutes after the Start of Andexanet Infusion**				**Hours Post Completion of Andexanet Infusion**													
Hour for Cohorts 1, 3, 5, 6:	**PRE**	**0**	**1**	**2**	**3**	**End Bolus (+2 min)**	**End Bolus (+5 min)**	**45 min**	**90 min**	**110 min**	**End Infu-sion (-2 min)**	**5 min**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4.5**	**5.5**	**6.5**	**7.5**	**8.5**	**14.5**
Hour for Cohort 2:	**PRE**	**0**	**1**	**2**	**4**																				
Hour for Cohorts 4, 7:	**PRE**	**0**	**1**		**1.5**																				
Hours for Cohorts 8-10:	**PRE**	**0**	**1**	**2**	**8**																				
Central Lab: Thrombin Generation	X				X	X	X	X	X	X	X	X	X	X	X	X		X		X		X			X	X
Central Lab: F1+2, TAT, D-dimer, Total TFPI, TFPI activity	X				X	X	X	X		X		X	X		X		X					X			X
Central Lab: tPA, PAP, TAFI, Free TFPI, β-TG, PF4, sTM	X				X	X	X	X		X		X	X		X		X					X			X
Fibrinogen, AT-III, FX	X				X	X	X	X		X		X	X												
VTE Screening																		X							
Concomitant Medication	X----------X																								
Adverse Events	X----------X																								

[1] qAM for edoxaban; q12h for apixaban and rivaroxaban. Window for dosing is ± 3 minutes.

[2] Last dose for all anticoagulants = Hour 0 (zero) on Day 6.

[3] IV will be in place 90 minutes pre-dose and for at least 3 hours post last dose of andexanet.

[4] To be completed after randomization but prior to administering andexanet as well as at 3 minutes and 10 minutes after the start of bolus administration.

Visit:	INPT		INPT		INPT	Discharge
Day:	**7**		**8**		**9**	**10**
	Hours Post Last Anticoagulant Dose					
	24	**36**	**48**	**60**	**0**	**0**
Physical Examination	X					X
Vital Signs (sitting)	X		X		X	X
12-lead ECG	X					X
Local Lab: Serum Chemistry	X					X
Local Lab: Hematology	X					X
Local Lab: Urinalysis	X					X
Local Lab: Serum Pregnancy						X
Stool (occult blood)	X		X		X	X
Central Lab: Anticoagulant PK (blood)	X		X		X	X
Central Lab: Andexanet PK (blood)	X		X		X	
Local Lab: PT, aPTT, ACT	X		X		X	X
Central Lab: Thrombin Generation	X				X	
Central Lab: Anti-fXa Activity	X		X		X	
Central Lab: F1+2, TAT, D-dimer, Total TFPI, TFPI activity	X		X		X	X
Central Lab: tPA, PAP, TAFI, Free TFPI, b-TG, PF4, sTM	X		X		X	X
Central Lab: Fibrinogen, AT-III, FX	X		X		X	X
VTE Screening	X					X
Concomitant Medication	X					
Adverse Events	X					

Visit:	OPV	Termination OPV
Day:	**20 (+3 days)**	**36 (+3 days)**
Physical Examination		X
Vital Signs (sitting)	X	X
12-lead ECG		X
Local Lab: Serum Chemistry		X
Local Lab: Hematology		X
Local Lab: Urinalysis		X
Local Lab: Serum Pregnancy		X
Local Lab: Urine (drugs of abuse)		X
Local Lab: Breathalyzer (Ethanol screen)		X
Central Lab: Thrombin Generation	X	X
Central Lab: F1+2, TAT, D-dimer, Total TFPI, TFPI Activity	X	X
Central Lab: tPA, PAP, TAFI, Free TFPI, b-TG, PF4, sTM	X	X
Central Lab: Fibrinogen, AT-III, FX	X	X
Central Lab: RVVT	X	X
Central Lab: Anti-fX, -fXa, -Andexanet Antibodies (neutralizing antibodies as appropriate)	X	X
VTE Screening	X	X
Concomitant Medication	X	X
Adverse Events	X	X

APPENDIX B. STUDY EVENTS FLOW CHART (PART 2)

Visit:	SCREENING [1]	ADMISSION	INPT	INPT	INPT	INPT
Day:	**≤ -45**	**-1**	**1**	**2**	**3**	**4**
Hour			0	0	0	0
Informed Consent	X					
Review/Complete I/E	X	X				
Medical History	X					
Medication History	X					
Physical Examination		X				
Vital Signs (sitting)	X	X	X	X	X	X
12-lead ECG	X					
Local Lab: Serum Chemistry	X					
Local Lab: Hematology	X	X				
Local Lab: Urinalysis	X					
Local Lab: Serum Pregnancy	X	X				
Local Lab: FSH	X					
Local Lab: Urine (drugs of abuse)		X				
Local Lab: Breathalyzer (Ethanol screen)		X				
Local Lab: Hep B & C, HIV I & II	X					
Local Lab: Factor V Leiden, Protein S&C, Anti-thrombin III	X					
Stool (occult blood) (if produced)	X	X	X	X	X	X
Randomization			X			
Administer Anticoagulant [2, 3]			X	X	X	X
Central Lab: Anticoagulant PK (blood)			X [4]			
Local Lab: PT, aPTT, ACT	X					
Central Lab: Thrombin generation			X [4]			
Central Lab: Anti-fXa activity			X [4]			
Central Lab: F1+2, TAT, D-dimer, TFPI activity			X [4]	X [5]	X [5]	X [5]
Central Lab: Anti-fX, Anti-fXa, Anti-andexanet Antibodies (Neutralizing Antibodies as appropriate)			X [4]			
VTE Screening	X	X				
Concomitant Medication		X----------				----------X
Adverse Events		X ----------				---------- X

[1] Screening activities may be done on more than one day.

[2] qAM for edoxaban; q12h for apixaban and rivaroxaban; Window for dosing is ± 3 minutes.

[3] Last dose for all anticoagulants = Hour 0 (zero) on Day 6.

[4] To be completed after randomization but prior to administering 1st dose of anticoagulant (Day 1) or andexanet.

[5] To be completed within 5 minutes prior to anticoagulant administration.

Visit:	**INPT**										
Day:	**5**										
Hour:	**PRE**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**12**
Physical Examination											
Vital Signs	X										
12-lead ECG	X										
Local Lab: Serum Chemistry	X										
Local Lab: Hematology	X										
Local Lab: Urinalysis	X										
Stool (occult blood)	X										
Administer Anticoagulant [1, 2]		X [2]									X [2]
Central Lab: Anticoagulant PK (blood)	X		X	X	X	X	X	X	X	X	X
Central Lab: Anti-fXa Activity	X		X [3]								
Central Lab: Thrombin Generation	X		X [3]								
Central Lab: F1+2, TAT, D-dimer, TFPI Activity	X		X [3]								
Concomitant Medication	X……X										
Adverse Events	X……X										

[1] qAM for edoxaban; q12h for apixaban and rivaroxaban. Window for dosing is ± 3 minutes.

[2] Last dose for all anticoagulants = Hour 0 (zero) on Day 6.

[3] These laboratory measurements should be performed 24 hours prior to the end of the andexanet/placebo continuous infusion on Day 6. For Cohorts 1, 3, 5, and 6, collection should be 3 hours after FXa inhibitor dosing. For Cohort 2, collection should be 4 hours after the FXa inhibitor dose. For Cohorts 4 and 7, collection should be 90 minutes after the FXa inhibitor dose. For Cohorts 8, 9, and 10, collection should be 8 hours after the FXa inhibitor dose.

Visit:	**INPT**																								
Day:	**6**																								
	Hours Post Anticoagulant Dose					**End of Bolus**		**Minutes after the Start of Andexanet Infusion**				**Hours Post Completion of Andexanet Infusion**													
Hour for Cohorts 1, 3, 5, 6:	**PRE**	**0**	**1**	**2**	**3**	**End Bolus (+2 min)**	**End Bolus (+5 min)**	**45 min**	**90 min**	**110 min**	**End Infu-sion (-2 min)**	**5 min**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4.5**	**5.5**	**6.5**	**7.5**	**8.5**	**14.5**
Hour for Cohort 2:	**PRE**	**0**	**1**	**2**	**4**																				
Hour for Cohorts 4, 7:	**PRE**	**0**	**1**		**1.5**																				
Hours for Cohorts 8-10:	**PRE**	**0**	**1**	**2**	**8**																				
Physical Examination	X																								
Vital Signs	X				X [4]	X	X	X				X													
Pulse Oximetry	X				X [4]	X	X	X				X													
12-lead ECG	X						X					X													
Local Lab: Serum Chemistry	X																								X
Local Lab: Hematology	X																								X
Local Lab: Urinalysis	X																								X
Stool (occult blood)						X																			
Administer Anticoagulant [1, 2]		X [2]																							
Administer Andexanet					X [3]	X……..…….....X																			
Central Lab: Anticoagulant PK (blood)	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X		X	X
Central Lab: Andexanet PK (blood)					X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Central Lab: Anti-fXa Activity	X				X	X	X	X	X	X	X	X	X	X	X		X		X		X	X		X	X

Visit	**INPT**																								
Day	**6**																								
	Hours Post Anticoagulant Dose					**End of Bolus**		**Minutes after the Start of Andexanet Infusion**				**Hours Post Completion of Andexanet Infusion**													
Hour for Cohorts 1, 3, 5, 6	**PRE**	**0**	**1**	**2**	**3**																				
Hour for Cohort 2	**PRE**	**0**	**1**	**2**	**4**	**End Bolus (+2 min)**	**End Bolus (+5 min)**	**45 min**	**90 min**	**110 min**	**End Infu-sion (-2 min)**	**5 min**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4.5**	**5.5**	**6.5**	**7.5**	**8.5**	**14.5**
Hour for Cohorts 4, 7	**PRE**	**0**	**1**		**1.5**																				
Hours for Cohorts 8-10:	**PRE**	**0**	**1**	**2**	**8**																				
Central Lab: Thrombin Generation	X				X	X	X	X	X	X	X	X	X	X	X		X		X		X	X		X	X
Central Lab: F1+2, TAT, D-dimer, TFPI activity	X				X	X	X	X		X		X	X		X		X					X			X
VTE Screening																		X							
Concomitant Medication	X----------X																								
Adverse Events	X----------X																								

[1] qAM for edoxaban; q12h for apixaban and rivaroxaban. Window for dosing is ± 3 minutes.

[2] Last dose for all anticoagulants = Hour 0 (zero) on Day 6.

[3] IV will be in place 90 minutes pre-dose and for at least 3 hours post last dose of andexanet.

[4] To be completed after randomization but prior to administering andexanet as well as at 3 minutes and 10 minutes after the start of bolus administration.

Visit:	INPT		INPT		INPT	Discharge
Day:	7		8		9	10
	Hours Post Last Anticoagulant Dose					
	24	36	48	60	0	0
Physical Examination	X					X
Vital Signs (sitting)	X		X		X	X
12-lead ECG	X					X
Local Lab: Serum Chemistry	X					X
Local Lab: Hematology	X					X
Local Lab: Urinalysis	X					X
Local Lab: Serum Pregnancy						X
Stool (occult blood)	X		X		X	X
Central Lab: Anticoagulant PK (blood)	X		X		X	X
Central Lab: Andexanet PK (blood)	X		X		X	
Central Lab: Thrombin Generation	X				X	
Central Lab: Anti-fXa Activity	X		X		X	
Central Lab: F1+2, TAT, D-dimer, TFPI activity	X		X		X	X
VTE Screening	X					X
Concomitant Medication	X					
Adverse Events	X					

Visit:	OPV	Termination OPV
Day:	20 (+3 days)	36 (+3 days)
Physical Examination		X
Vital Signs (sitting)	X	X
12-lead ECG		X
Local Lab: Serum Chemistry		X
Local Lab: Hematology		X
Local Lab: Urinalysis		X
Local Lab: Serum Pregnancy		X
Local Lab: Urine (drugs of abuse)		X
Local Lab: Breathalyzer (Ethanol screen)		X
Central Lab: Thrombin Generation	X	X
Central Lab: F1+2, TAT, D-dimer, TFPI Activity	X	X
Central Lab: Anti-fX, -fXa, -Andexanet Antibodies (neutralizing antibodies as appropriate)	X	X
VTE Screening	X	X
Concomitant Medication	X	X
Adverse Events	X	X

APPENDIX C. WELLS SCORES

Clinical risk scores [7] for assessing the probability of Pulmonary Embolism (PE)

Parameter	Score
Wells score [1] for Prediction of PE (Wells)	
Clinically Suspected DVT	3
Alternative Diagnosis Less Likely than PE	3
Heart Rate Greater than 100	1.5
Immobilization within Past 4 weeks	1.5
History of DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment, treated in the last 6 months, or palliative)	1

[1] A total score > 6 indicates a high probability of a PE, 2–6 moderate probability and < 2 low probability.

Clinical risk scores [8] for assessing the probability of deep vein thrombosis (DVT)

Parameter	Score
Entire Leg Swollen	1
Calf Swelling 3 cm > Asymptomatic Side	1
Pitting Edema Confined to Symptomatic Leg	1
Localized Tenderness Along Distribution of Deep Vein System	1
Collateral Superficial Veins (non-varicose)	1
Active Cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, Paresis, or Recent Plaster Immobilization of Legs	1
Recent Immobilization > 3 days or Major Surgery within 4 Weeks	1
Alternative Diagnosis as Likely or Greater than That of DVT	-2

Notes: Clinical probability: HIGH (3); MODERATE (1 or 2); LOW (0).
HIGH > 75% incidence DVT; LOW < 5% incidence.

APPENDIX D. US PACKAGE INSERT FOR APIXABAN (ELIQUIS)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ELIQUIS safely and effectively. See full prescribing information for ELIQUIS.

ELIQUIS® (apixaban) tablets, for oral use

Initial U.S. Approval: 2012

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

(B) SPINAL/EPIDURAL HEMATOMA

See full prescribing information for complete boxed warning.

(A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS: Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy. (2.4, 5.1, 14.1)

(B) SPINAL/EPIDURAL HEMATOMA: Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. (5.3)

RECENT MAJOR CHANGES

Dosage and Administration (2.6)	7/2016
Warnings and Precautions (5.2)	7/2016

INDICATIONS AND USAGE

ELIQUIS is a factor Xa inhibitor indicated:

- to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. (1.1)
- for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery. (1.2)
- for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy. (1.3, 1.4, 1.5)

DOSAGE AND ADMINISTRATION

- Reduction of risk of stroke and systemic embolism in nonvalvular atrial fibrillation:
  - The recommended dose is 5 mg orally twice daily. (2.1)
  - In patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily. (2.1)
- Prophylaxis of DVT following hip or knee replacement surgery:
  - The recommended dose is 2.5 mg orally twice daily. (2.1)
- Treatment of DVT and PE:
  - The recommended dose is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily. (2.1)
- Reduction in the risk of recurrent DVT and PE following initial therapy:
  - The recommended dose is 2.5 mg taken orally twice daily. (2.1)

DOSAGE FORMS AND STRENGTHS

- Tablets: 2.5 mg and 5 mg (3)

CONTRAINDICATIONS

- Active pathological bleeding (4)
- Severe hypersensitivity to ELIQUIS (apixaban) (4)

WARNINGS AND PRECAUTIONS

- ELIQUIS can cause serious, potentially fatal bleeding. Promptly evaluate signs and symptoms of blood loss. (5.2)
- Prosthetic heart valves: ELIQUIS use not recommended. (5.4)

ADVERSE REACTIONS

Most common adverse reactions (>1%) are related to bleeding. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Strong dual inhibitors of CYP3A4 and P-gp increase blood levels of apixaban. Reduce ELIQUIS dose or avoid coadministration. (2.5, 7.1, 12.3)
- Simultaneous use of strong dual inducers of CYP3A4 and P-gp reduces blood levels of apixaban: Avoid concomitant use. (7.2, 12.3)

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* Not recommended. (8.1)
- *Nursing Mothers:* Discontinue drug or discontinue nursing. (8.3)
- *Severe Hepatic Impairment:* Not recommended. (8.7, 12.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

(B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.4), Warnings and Precautions (5.1), and Clinical Studies (14.1)]*.

(B) SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

[see Warnings and Precautions (5.3)]

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions (5.3)]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

1.1 Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

ELIQUIS® (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

1.2 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

ELIQUIS is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

1.3 Treatment of Deep Vein Thrombosis

ELIQUIS is indicated for the treatment of DVT.

1.4 Treatment of Pulmonary Embolism

ELIQUIS is indicated for the treatment of PE.

1.5 Reduction in the Risk of Recurrence of DVT and PE

ELIQUIS is indicated to reduce the risk of recurrent DVT and PE following initial therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The recommended dose of ELIQUIS for most patients is 5 mg taken orally twice daily.

The recommended dose of ELIQUIS is 2.5 mg twice daily in patients with at least two of the following characteristics:

- age ≥80 years
- body weight ≤60 kg
- serum creatinine ≥1.5 mg/dL

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The recommended dose of ELIQUIS is 2.5 mg taken orally twice daily. The initial dose should be taken 12 to 24 hours after surgery.

- In patients undergoing hip replacement surgery, the recommended duration of treatment is 35 days.
- In patients undergoing knee replacement surgery, the recommended duration of treatment is 12 days.

Treatment of DVT and PE

The recommended dose of ELIQUIS is 10 mg taken orally twice daily for the first 7 days of therapy. After 7 days, the recommended dose is 5 mg taken orally twice daily.

Reduction in the Risk of Recurrence of DVT and PE

The recommended dose of ELIQUIS is 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE *[see Clinical Studies (14.3)]*.

2.2 Missed Dose

If a dose of ELIQUIS is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and twice-daily administration should be resumed. The dose should not be doubled to make up for a missed dose.

2.3 Temporary Interruption for Surgery and Other Interventions

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

2.4 Converting from or to ELIQUIS

Switching from warfarin to ELIQUIS: Warfarin should be discontinued and ELIQUIS started when the international normalized ratio (INR) is below 2.0.

Switching from ELIQUIS to warfarin: ELIQUIS affects INR, so that initial INR measurements during the transition to warfarin may not be useful for determining the appropriate dose of warfarin. One approach is to discontinue ELIQUIS and begin both a parenteral anticoagulant and warfarin at the time the next dose of ELIQUIS would have been taken, discontinuing the parenteral anticoagulant when INR reaches an acceptable range.

Switching from ELIQUIS to anticoagulants other than warfarin (oral or parenteral): Discontinue ELIQUIS and begin taking the new anticoagulant other than warfarin at the usual time of the next dose of ELIQUIS.

Switching from anticoagulants other than warfarin (oral or parenteral) to ELIQUIS: Discontinue the anticoagulant other than warfarin and begin taking ELIQUIS at the usual time of the next dose of the anticoagulant other than warfarin.

2.5 Strong Dual Inhibitors of CYP3A4 and P-glycoprotein

For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose by 50% when ELIQUIS is coadministered with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin) *[see Clinical Pharmacology (12.3)]*.

In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp *[see Drug Interactions (7.1)]*.

2.6 Administration Options

For patients who are unable to swallow whole tablets, 5 mg and 2.5 mg ELIQUIS tablets may be crushed and suspended in water, 5% dextrose in water (D5W), or apple juice, or mixed with applesauce and promptly administered orally *[see Clinical Pharmacology (12.3)]*. Alternatively, ELIQUIS tablets may be crushed and suspended in 60 mL of water or D5W and promptly delivered through a nasogastric tube *[see Clinical Pharmacology (12.3)]*.

Crushed ELIQUIS tablets are stable in water, D5W, apple juice, and applesauce for up to 4 hours.

3 DOSAGE FORMS AND STRENGTHS

- 2.5 mg, yellow, round, biconvex, film-coated tablets with “893” debossed on one side and “2½” on the other side.
- 5 mg, pink, oval-shaped, biconvex, film-coated tablets with “894” debossed on one side and “5” on the other side.

4 CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

- Active pathological bleeding *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions) *[see Adverse Reactions (6.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.4) and Clinical Studies (14.1)]*.

5.2 Bleeding

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding *[see Dosage and Administration (2.1) and Adverse Reactions (6.1)]*.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions (7.3)]*.

Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.

Reversal of Anticoagulant Effect

A specific antidote for ELIQUIS is not available, and there is no established way to reverse bleeding in patients taking ELIQUIS. The pharmacodynamic effect of ELIQUIS can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. Use of procoagulant reversal agents, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa, may be considered but has not been evaluated in clinical studies *[see Clinical Pharmacology (12.2)]*. When PCCs are used, monitoring for the anticoagulation effect of apixaban using a clotting test (PT, INR, or aPTT) or anti-factor Xa (FXa) activity is not useful and is not recommended. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration *[see Overdosage (10)]*.

Hemodialysis does not appear to have a substantial impact on apixaban exposure *[see Clinical Pharmacology (12.3)]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is no experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban and they are not expected to be effective as a reversal agent.

5.3 Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel, or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

5.4 Patients with Prosthetic Heart Valves

The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves. Therefore, use of ELIQUIS is not recommended in these patients.

5.5 Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy

Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information.

- Increased risk of thrombotic events after premature discontinuation *[see Warnings and Precautions (5.1)]*
- Bleeding *[see Warnings and Precautions (5.2)]*
- Spinal/epidural anesthesia or puncture *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The safety of ELIQUIS was evaluated in the ARISTOTLE and AVERROES studies *[see Clinical Studies (14)]*, including 11,284 patients exposed to ELIQUIS 5 mg twice daily and 602 patients exposed to ELIQUIS 2.5 mg twice daily. The duration of ELIQUIS exposure was ≥12 months for 9375 patients and ≥24 months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks (>15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (>3000 patient-years).

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The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on ELIQUIS and aspirin, respectively.

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

Tables 1 and 2 show the number of patients experiencing major bleeding during the treatment period and the bleeding rate (percentage of subjects with at least one bleeding event per 100 patient-years) in ARISTOTLE and AVERROES.

Table 1: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE*

	ELIQUIS N=9088 n (per 100 pt-year)	Warfarin N=9052 n (per 100 pt-year)	Hazard Ratio (95% CI)	P-value
Major†	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001
Intracranial (ICH)‡	52 (0.33)	125 (0.82)	0.41 (0.30, 0.57)	-
Hemorrhagic stroke§	38 (0.24)	74 (0.49)	0.51 (0.34, 0.75)	-
Other ICH	15 (0.10)	51 (0.34)	0.29 (0.16, 0.51)	-
Gastrointestinal (GI)¶	128 (0.83)	141 (0.93)	0.89 (0.70, 1.14)	-
Fatal**	10 (0.06)	37 (0.24)	0.27 (0.13, 0.53)	-
Intracranial	4 (0.03)	30 (0.20)	0.13 (0.05, 0.37)	-
Non-intracranial	6 (0.04)	7 (0.05)	0.84 (0.28, 2.15)	-

* Bleeding events within each subcategory were counted once per subject, but subjects may have contributed events to multiple endpoints. Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period).

† Defined as clinically overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal or with fatal outcome.

‡ Intracranial bleed includes intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as an intracranial major bleed.

§ On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14.

¶ GI bleed includes upper GI, lower GI, and rectal bleeding.

** Fatal bleeding is an adjudicated death with the primary cause of death as intracranial bleeding or non-intracranial bleeding during the on-treatment period.

In ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, $CHADS_2$ score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, and aspirin use at randomization (Figure 1). Subjects treated with apixaban with diabetes bled more (3.0% per year) than did subjects without diabetes (1.9% per year).

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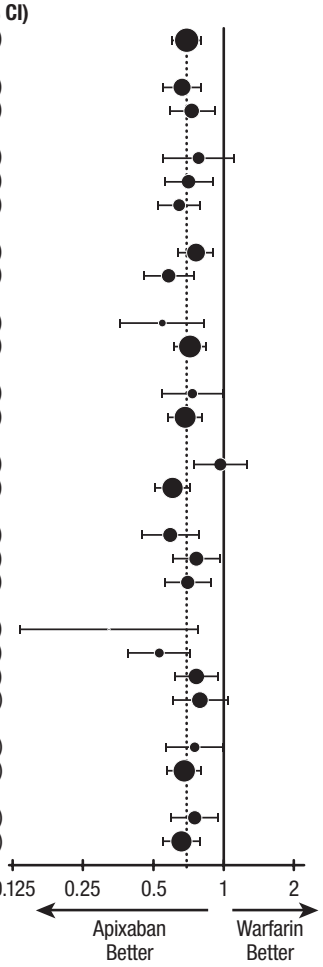
Figure 1: Major Bleeding Hazard Ratios by Baseline Characteristics – ARISTOTLE Study

Subgroup	n of Events / N of Patients (% per year) Apixaban	Warfarin	Hazard Ratio (95% CI)
All Patients	327 / 9088 (2.1)	462 / 9052 (3.1)	0.69 (0.60, 0.80)
Prior Warfarin/VKA Status			
Experienced (57%)	185 / 5196 (2.1)	274 / 5180 (3.2)	0.66 (0.55, 0.80)
Naive (43%)	142 / 3892 (2.2)	188 / 3872 (3.0)	0.73 (0.59, 0.91)
Age			
<65 (30%)	56 / 2723 (1.2)	72 / 2732 (1.5)	0.78 (0.55, 1.11)
≥65 and <75 (39%)	120 / 3529 (2.0)	166 / 3501 (2.8)	0.71 (0.56, 0.89)
≥75 (31%)	151 / 2836 (3.3)	224 / 2819 (5.2)	0.64 (0.52, 0.79)
Sex			
Male (65%)	225 / 5868 (2.3)	294 / 5879 (3.0)	0.76 (0.64, 0.90)
Female (35%)	102 / 3220 (1.9)	168 / 3173 (3.3)	0.58 (0.45, 0.74)
Weight			
≤60 kg (11%)	36 / 1013 (2.3)	62 / 965 (4.3)	0.55 (0.36, 0.83)
>60 kg (89%)	290 / 8043 (2.1)	398 / 8059 (3.0)	0.72 (0.62, 0.83)
Prior Stroke or TIA			
Yes (19%)	77 / 1687 (2.8)	106 / 1735 (3.9)	0.73 (0.54, 0.98)
No (81%)	250 / 7401 (2.0)	356 / 7317 (2.9)	0.68 (0.58, 0.80)
Diabetes Mellitus			
Yes (25%)	112 / 2276 (3.0)	114 / 2250 (3.1)	0.96 (0.74, 1.25)
No (75%)	215 / 6812 (1.9)	348 / 6802 (3.1)	0.60 (0.51, 0.71)
$CHADS_2$ Score			
≤1 (34%)	76 / 3093 (1.4)	126 / 3076 (2.3)	0.59 (0.44, 0.78)
2 (36%)	125 / 3246 (2.3)	163 / 3246 (3.0)	0.76 (0.60, 0.96)
≥3 (30%)	126 / 2749 (2.9)	173 / 2730 (4.1)	0.70 (0.56, 0.88)
Creatinine Clearance			
<30 mL/min (1%)	7 / 136 (3.7)	19 / 132 (11.9)	0.32 (0.13, 0.78)
30-50 mL/min (15%)	66 / 1357 (3.2)	123 / 1380 (6.0)	0.53 (0.39, 0.71)
>50-80 mL/min (42%)	157 / 3807 (2.5)	199 / 3758 (3.2)	0.76 (0.62, 0.94)
>80 mL/min (41%)	96 / 3750 (1.5)	119 / 3746 (1.8)	0.79 (0.61, 1.04)
Geographic Region			
US (19%)	83 / 1716 (2.8)	109 / 1693 (3.8)	0.75 (0.56, 1.00)
Non-US (81%)	244 / 7372 (2.0)	353 / 7359 (2.9)	0.68 (0.57, 0.80)
Aspirin at Randomization			
Yes (31%)	129 / 2846 (2.7)	164 / 2762 (3.7)	0.75 (0.60, 0.95)
No (69%)	198 / 6242 (1.9)	298 / 6290 (2.8)	0.66 (0.55, 0.79)



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were pre-specified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Table 2: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	ELIQUIS N=2798 n (%/year)	Aspirin N=2780 n (%/year)	Hazard Ratio (95% CI)	P-value
Major	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.07
Fatal	5 (0.16)	5 (0.16)	0.99 (0.23, 4.29)	-
Intracranial	11 (0.34)	11 (0.35)	0.99 (0.39, 2.51)	-

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Other Adverse Reactions

Hypersensitivity reactions (including drug hypersensitivity, such as skin rash, and anaphylactic reactions, such as allergic edema) and syncope were reported in <1% of patients receiving ELIQUIS.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The safety of ELIQUIS has been evaluated in 1 Phase II and 3 Phase III studies including 5924 patients exposed to ELIQUIS 2.5 mg twice daily undergoing major orthopedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days.

In total, 11% of the patients treated with ELIQUIS 2.5 mg twice daily experienced adverse reactions.

Bleeding results during the treatment period in the Phase III studies are shown in Table 3. Bleeding was assessed in each study beginning with the first dose of double-blind study drug.

Table 3: Bleeding During the Treatment Period in Patients Undergoing Elective Hip or Knee Replacement Surgery

Bleeding Endpoint*	ADVANCE-3 Hip Replacement Surgery		ADVANCE-2 Knee Replacement Surgery		ADVANCE-1 Knee Replacement Surgery	
	ELIQUIS 2.5 mg po bid 35±3 days	Enoxaparin 40 mg sc qd 35±3 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 40 mg sc qd 12±2 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 30 mg sc q12h 12±2 days
	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 12 to 24 hours post surgery
All treated	N=2673	N=2659	N=1501	N=1508	N=1596	N=1588
Major (including surgical site)	22 (0.82%)†	18 (0.68%)	9 (0.60%)‡	14 (0.93%)	11 (0.69%)	22 (1.39%)
Fatal	0	0	0	0	0	1 (0.06%)
Hgb decrease ≥2 g/dL	13 (0.49%)	10 (0.38%)	8 (0.53%)	9 (0.60%)	10 (0.63%)	16 (1.01%)
Transfusion of ≥2 units RBC	16 (0.60%)	14 (0.53%)	5 (0.33%)	9 (0.60%)	9 (0.56%)	18 (1.13%)

(Continued)

Table 3: *(Continued)* **Bleeding During the Treatment Period in Patients Undergoing Elective Hip or Knee Replacement Surgery**

Bleeding Endpoint*	ADVANCE-3 Hip Replacement Surgery		ADVANCE-2 Knee Replacement Surgery		ADVANCE-1 Knee Replacement Surgery	
	ELIQUIS 2.5 mg po bid 35±3 days	Enoxaparin 40 mg sc qd 35±3 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 40 mg sc qd 12±2 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 30 mg sc q12h 12±2 days
	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 12 to 24 hours post surgery
Bleed at critical site§	1 (0.04%)	1 (0.04%)	1 (0.07%)	2 (0.13%)	1 (0.06%)	4 (0.25%)
Major + CRNM¶	129 (4.83%)	134 (5.04%)	53 (3.53%)	72 (4.77%)	46 (2.88%)	68 (4.28%)
All	313 (11.71%)	334 (12.56%)	104 (6.93%)	126 (8.36%)	85 (5.33%)	108 (6.80%)

*All bleeding criteria included surgical site bleeding.

†Includes 13 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).

‡Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).

§Intracranial, intraspinal, intraocular, pericardial, an operated joint requiring re-operation or intervention, intramuscular with compartment syndrome, or retroperitoneal. Bleeding into an operated joint requiring re-operation or intervention was present in all patients with this category of bleeding. Events and event rates include one enoxaparin-treated patient in ADVANCE-1 who also had intracranial hemorrhage.

¶CRNM = clinically relevant nonmajor.

Adverse reactions occurring in ≥1% of patients undergoing hip or knee replacement surgery in the 1 Phase II study and the 3 Phase III studies are listed in Table 4.

Table 4: **Adverse Reactions Occurring in ≥1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery**

	ELIQUIS, n (%) 2.5 mg po bid N=5924	Enoxaparin, n (%) 40 mg sc qd or 30 mg sc q12h N=5904
Nausea	153 (2.6)	159 (2.7)
Anemia (including postoperative and hemorrhagic anemia, and respective laboratory parameters)	153 (2.6)	178 (3.0)
Contusion	83 (1.4)	115 (1.9)
Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)	67 (1.1)	81 (1.4)
Postprocedural hemorrhage (including postprocedural hematoma, wound hemorrhage, vessel puncture site hematoma and catheter site hemorrhage)	54 (0.9)	60 (1.0)
Transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal)	50 (0.8)	71 (1.2)
Aspartate aminotransferase increased	47 (0.8)	69 (1.2)
Gamma-glutamyltransferase increased	38 (0.6)	65 (1.1)

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: thrombocytopenia (including platelet count decreases)

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

Gastrointestinal disorders: gastrointestinal hemorrhage (including hematemesis and melena), hematochezia

Hepatobiliary disorders: liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased

Renal and urinary disorders: hematuria (including respective laboratory parameters)

Injury, poisoning, and procedural complications: wound secretion, incision-site hemorrhage (including incision-site hematoma), operative hemorrhage

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Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of <0.1%:

Gingival bleeding, hemoptysis, hypersensitivity, muscle hemorrhage, ocular hemorrhage (including conjunctival hemorrhage), rectal hemorrhage

Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT or PE

The safety of ELIQUIS has been evaluated in the AMPLIFY and AMPLIFY-EXT studies, including 2676 patients exposed to ELIQUIS 10 mg twice daily, 3359 patients exposed to ELIQUIS 5 mg twice daily, and 840 patients exposed to ELIQUIS 2.5 mg twice daily.

Common adverse reactions (≥1%) were gingival bleeding, epistaxis, contusion, hematuria, rectal hemorrhage, hematoma, menorrhagia, and hemoptysis.

AMPLIFY Study

The mean duration of exposure to ELIQUIS was 154 days and to enoxaparin/warfarin was 152 days in the AMPLIFY study. Adverse reactions related to bleeding occurred in 417 (15.6%) ELIQUIS-treated patients compared to 661 (24.6%) enoxaparin/warfarin-treated patients. The discontinuation rate due to bleeding events was 0.7% in the ELIQUIS-treated patients compared to 1.7% in enoxaparin/warfarin-treated patients in the AMPLIFY study.

In the AMPLIFY study, ELIQUIS was statistically superior to enoxaparin/warfarin in the primary safety endpoint of major bleeding (relative risk 0.31, 95% CI [0.17, 0.55], P-value <0.0001).

Bleeding results from the AMPLIFY study are summarized in Table 5.

Table 5: **Bleeding Results in the AMPLIFY Study**

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)	Relative Risk (95% CI)
Major	15 (0.6)	49 (1.8)	0.31 (0.17, 0.55) p<0.0001
CRNM*	103 (3.9)	215 (8.0)	
Major + CRNM	115 (4.3)	261 (9.7)	
Minor	313 (11.7)	505 (18.8)	
All	402 (15.0)	676 (25.1)	

*CRNM = clinically relevant nonmajor bleeding.

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY study are listed in Table 6.

Table 6: **Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study**

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)
Epistaxis	77 (2.9)	146 (5.4)
Contusion	49 (1.8)	97 (3.6)
Hematuria	46 (1.7)	102 (3.8)
Menorrhagia	38 (1.4)	30 (1.1)
Hematoma	35 (1.3)	76 (2.8)
Hemoptysis	32 (1.2)	31 (1.2)
Rectal hemorrhage	26 (1.0)	39 (1.5)
Gingival bleeding	26 (1.0)	50 (1.9)

AMPLIFY-EXT Study

The mean duration of exposure to ELIQUIS was approximately 330 days and to placebo was 312 days in the AMPLIFY-EXT study. Adverse reactions related to bleeding occurred in 219 (13.3%) ELIQUIS-treated patients compared to 72 (8.7%) placebo-treated patients. The discontinuation rate due to bleeding events was approximately 1% in the ELIQUIS-treated patients compared to 0.4% in those patients in the placebo group in the AMPLIFY-EXT study.

Bleeding results from the AMPLIFY-EXT study are summarized in Table 7.

Table 7: Bleeding Results in the AMPLIFY-EXT Study

	ELIQUIS 2.5 mg bid N=840 n (%)	ELIQUIS 5 mg bid N=811 n (%)	Placebo N=826 n (%)
Major	2 (0.2)	1 (0.1)	4 (0.5)
CRNM*	25 (3.0)	34 (4.2)	19 (2.3)
Major + CRNM	27 (3.2)	35 (4.3)	22 (2.7)
Minor	75 (8.9)	98 (12.1)	58 (7.0)
All	94 (11.2)	121 (14.9)	74 (9.0)

*CRNM = clinically relevant nonmajor bleeding.

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY-EXT study are listed in Table 8.

Table 8: Adverse Reactions Occurring in ≥1% of Patients Undergoing Extended Treatment for DVT and PE in the AMPLIFY-EXT Study

	ELIQUIS 2.5 mg bid N=840 n (%)	ELIQUIS 5 mg bid N=811 n (%)	Placebo N=826 n (%)
Epistaxis	13 (1.5)	29 (3.6)	9 (1.1)
Hematuria	12 (1.4)	17 (2.1)	9 (1.1)
Hematoma	13 (1.5)	16 (2.0)	10 (1.2)
Contusion	18 (2.1)	18 (2.2)	18 (2.2)
Gingival bleeding	12 (1.4)	9 (1.1)	3 (0.4)

Other Adverse Reactions

Less common adverse reactions in ELIQUIS-treated patients in the AMPLIFY or AMPLIFY-EXT studies occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: hemorrhagic anemia

Gastrointestinal disorders: hematochezia, hemorrhoidal hemorrhage, gastrointestinal hemorrhage, hematemesis, melena, anal hemorrhage

Injury, poisoning, and procedural complications: wound hemorrhage, postprocedural hemorrhage, traumatic hematoma, periorbital hematoma

Musculoskeletal and connective tissue disorders: muscle hemorrhage

Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia, menometrorrhagia, genital hemorrhage

Vascular disorders: hemorrhage

Skin and subcutaneous tissue disorders: ecchymosis, skin hemorrhage, petechiae

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

Investigations: blood urine present, occult blood positive, occult blood, red blood cells urine positive

General disorders and administration-site conditions: injection-site hematoma, vessel puncture-site hematoma

7 DRUG INTERACTIONS

Apixaban is a substrate of both CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.

7.1 Strong Dual Inhibitors of CYP3A4 and P-gp

For patients receiving ELIQUIS 5 mg or 10 mg twice daily, the dose of ELIQUIS should be decreased by 50% when coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

For patients receiving ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with strong dual inhibitors of CYP3A4 and P-gp *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

7.2 Strong Dual Inducers of CYP3A4 and P-gp

Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban *[see Clinical Pharmacology (12.3)]*.

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7.3 Anticoagulants and Antiplatelet Agents

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk, post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo. The rate of ISTH major bleeding was 2.8% per year with apixaban versus 0.6% per year with placebo in patients receiving single antiplatelet therapy and was 5.9% per year with apixaban versus 2.5% per year with placebo in those receiving dual antiplatelet therapy.

In ARISTOTLE, concomitant use of aspirin increased the bleeding risk on ELIQUIS from 1.8% per year to 3.4% per year and concomitant use of aspirin and warfarin increased the bleeding risk from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of dual antiplatelet therapy with ELIQUIS.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Treatment of pregnant rats, rabbits, and mice after implantation until the end of gestation resulted in fetal exposure to apixaban, but was not associated with increased risk for fetal malformations or toxicity. No maternal or fetal deaths were attributed to bleeding. Increased incidence of maternal bleeding was observed in mice, rats, and rabbits at maternal exposures that were 19, 4, and 1 times, respectively, the human exposure of unbound drug, based on area under plasma-concentration time curve (AUC) comparisons at the maximum recommended human dose (MRHD) of 10 mg (5 mg twice daily).

8.2 Labor and Delivery

Safety and effectiveness of ELIQUIS during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using ELIQUIS in this setting *[see Warnings and Precautions (5.2)]*.

Treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with apixaban at a dose of 1000 mg/kg (about 5 times the human exposure based on unbound apixaban) did not result in death of offspring or death of mother rats during labor in association with uterine bleeding. However, increased incidence of maternal bleeding, primarily during gestation, occurred at apixaban doses of ≥25 mg/kg, a dose corresponding to ≥1.3 times the human exposure.

8.3 Nursing Mothers

It is unknown whether apixaban or its metabolites are excreted in human milk. Rats excrete apixaban in milk (12% of the maternal dose).

Women should be instructed either to discontinue breastfeeding or to discontinue ELIQUIS therapy, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total subjects in the ARISTOTLE and AVERROES clinical studies, >69% were 65 and older, and >31% were 75 and older. In the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical studies, 50% of subjects were 65 and older, while 16% were 75 and older. In the AMPLIFY and AMPLIFY-EXT clinical studies, >32% of subjects were 65 and older and >13% were 75 and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

8.6 Renal Impairment

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The recommended dose is 2.5 mg twice daily in patients with at least two of the following characteristics *[see Dosage and Administration (2.1)]*:

- age ≥80 years
- body weight ≤60 kg
- serum creatinine ≥1.5 mg/dL

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of ELIQUIS at the usually recommended dose *[see Dosage and Administration (2.1)]* will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study *[see Clinical Pharmacology (12.3)]*. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery, and Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT and PE

No dose adjustment is recommended for patients with renal impairment, including those with ESRD on dialysis *[see Dosage and Administration (2.1)]*. Clinical efficacy and safety studies with ELIQUIS did not enroll patients with ESRD on dialysis or patients with a CrCl <15 mL/min; therefore, dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-FXa activity) data in subjects with ESRD maintained on dialysis *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A).

Because patients with moderate hepatic impairment (Child-Pugh class B) may have intrinsic coagulation abnormalities and there is limited clinical experience with ELIQUIS in these patients, dosing recommendations cannot be provided *[see Clinical Pharmacology (12.2)]*.

ELIQUIS is not recommended in patients with severe hepatic impairment (Child-Pugh class C) *[see Clinical Pharmacology (12.2)]*.

10 OVERDOSAGE

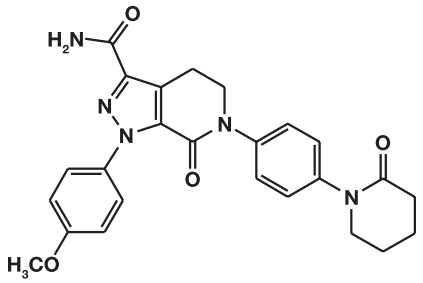
There is no antidote to ELIQUIS. Overdose of ELIQUIS increases the risk of bleeding *[see Warnings and Precautions (5.2)]*.

In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily for 7 days or 50 mg once daily for 3 days) had no clinically relevant adverse effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

11 DESCRIPTION

ELIQUIS (apixaban), a factor Xa (FXa) inhibitor, is chemically described as 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide. Its molecular formula is $C_{25}H_{25}N_5O_4$, which corresponds to a molecular weight of 459.5. Apixaban has the following structural formula:



Apixaban is a white to pale-yellow powder. At physiological pH (1.2–6.8), apixaban does not ionize; its aqueous solubility across the physiological pH range is ~0.04 mg/mL.

ELIQUIS tablets are available for oral administration in strengths of 2.5 mg and 5 mg of apixaban with the following inactive ingredients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate. The film coating contains lactose monohydrate, hypromellose, titanium dioxide, triacetin, and yellow iron oxide (2.5 mg tablets) or red iron oxide (5 mg tablets).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Apixaban is a selective inhibitor of FXa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound FXa, and prothrombinase activity. Apixaban has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, apixaban decreases thrombin generation and thrombus development.

12.2 Pharmacodynamics

As a result of FXa inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests at the expected therapeutic dose, however, are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of apixaban.

The Rotachrom® Heparin chromogenic assay was used to measure the effect of apixaban on FXa activity in humans during the apixaban development program. A concentration-dependent increase in anti-FXa activity was observed in the dose range tested and was similar in healthy subjects and patients with AF.

This test is not recommended for assessing the anticoagulant effect of apixaban.

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Effect of PCCs on Pharmacodynamics of ELIQUIS

There is no clinical experience to reverse bleeding with the use of 4-factor PCC products in individuals who have received ELIQUIS.

Effects of 4-factor PCCs on the pharmacodynamics of apixaban were studied in healthy subjects. Following administration of apixaban dosed to steady state, endogenous thrombin potential (ETP) returned to pre-apixaban levels 4 hours after the initiation of a 30 minute PCC infusion, compared to 45 hours with placebo. Mean ETP levels continued to increase and exceeded pre-apixaban levels reaching a maximum (34 - 51% increase over pre-apixaban levels) at 21 hours after initiating PCC and remained elevated (21 – 27% increase) at the end of the study (69 hours after initiation of PCC). The clinical relevance of this increase in ETP is unknown.

Pharmacodynamic Drug Interaction Studies

Pharmacodynamic drug interaction studies with aspirin, clopidogrel, aspirin and clopidogrel, prasugrel, enoxaparin, and naproxen were conducted. No pharmacodynamic interactions were observed with aspirin, clopidogrel, or prasugrel *[see Warnings and Precautions (5.2)]*. A 50% to 60% increase in anti-FXa activity was observed when apixaban was coadministered with enoxaparin or naproxen.

Specific Populations

Renal impairment: Anti-FXa activity adjusted for exposure to apixaban was similar across renal function categories.

Hepatic impairment: Changes in anti-FXa activity were similar in patients with mild-to-moderate hepatic impairment and healthy subjects. However, in patients with moderate hepatic impairment, there is no clear understanding of the impact of this degree of hepatic function impairment on the coagulation cascade and its relationship to efficacy and bleeding. Patients with severe hepatic impairment were not studied.

Cardiac Electrophysiology

Apixaban has no effect on the QTc interval in humans at doses up to 50 mg.

12.3 Pharmacokinetics

Apixaban demonstrates linear pharmacokinetics with dose-proportional increases in exposure for oral doses up to 10 mg.

Absorption

The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg of ELIQUIS. Food does not affect the bioavailability of apixaban. Maximum concentrations (C_{max}) of apixaban appear 3 to 4 hours after oral administration of ELIQUIS. At doses ≥25 mg, apixaban displays dissolution-limited absorption with decreased bioavailability. Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets suspended in 30 mL of water, exposure was similar to that after oral administration of 2 intact 5 mg tablets. Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets mixed with 30 g of applesauce, the C_{max} and AUC were 20% and 16% lower, respectively, when compared to administration of 2 intact 5 mg tablets. Following administration of a crushed 5 mg ELIQUIS tablet that was suspended in 60 mL D5W and delivered through a nasogastric tube, exposure was similar to that seen in other clinical trials involving healthy volunteers receiving a single oral 5 mg tablet dose.

Distribution

Plasma protein binding in humans is approximately 87%. The volume of distribution (Vss) is approximately 21 liters.

Metabolism

Approximately 25% of an orally administered apixaban dose is recovered in urine and feces as metabolites. Apixaban is metabolized mainly via CYP3A4 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation.

Unchanged apixaban is the major drug-related component in human plasma; there are no active circulating metabolites.

Elimination

Apixaban is eliminated in both urine and feces. Renal excretion accounts for about 27% of total clearance. Biliary and direct intestinal excretion contributes to elimination of apixaban in the feces.

Apixaban has a total clearance of approximately 3.3 L/hour and an apparent half-life of approximately 12 hours following oral administration.

Apixaban is a substrate of transport proteins: P-gp and breast cancer resistance protein.

Drug Interaction Studies

In vitro apixaban studies at concentrations significantly greater than therapeutic exposures, no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP3A4/5, or CYP2C19, nor induction effect on the activity of CYP1A2, CYP2B6, or CYP3A4/5 were observed. Therefore, apixaban is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Apixaban is not a significant inhibitor of P-gp.

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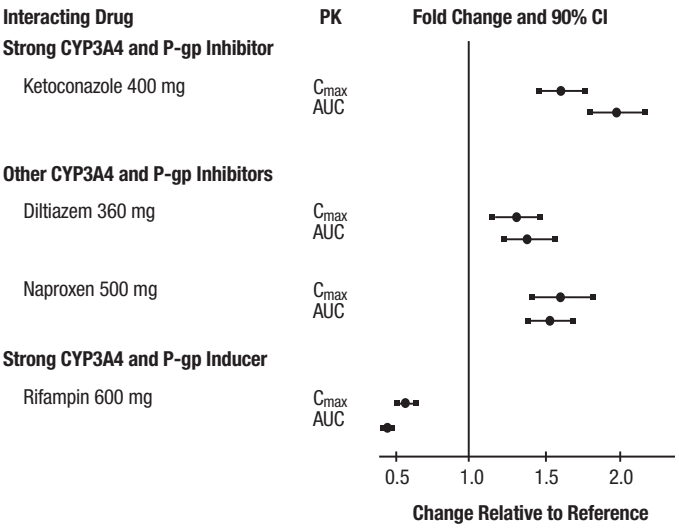
The effects of coadministered drugs on the pharmacokinetics of apixaban are summarized in Figure 2 *[see also Warnings and Precautions (5.2) and Drug Interactions (7)]*.

Figure 2: Effect of Coadministered Drugs on the Pharmacokinetics of Apixaban



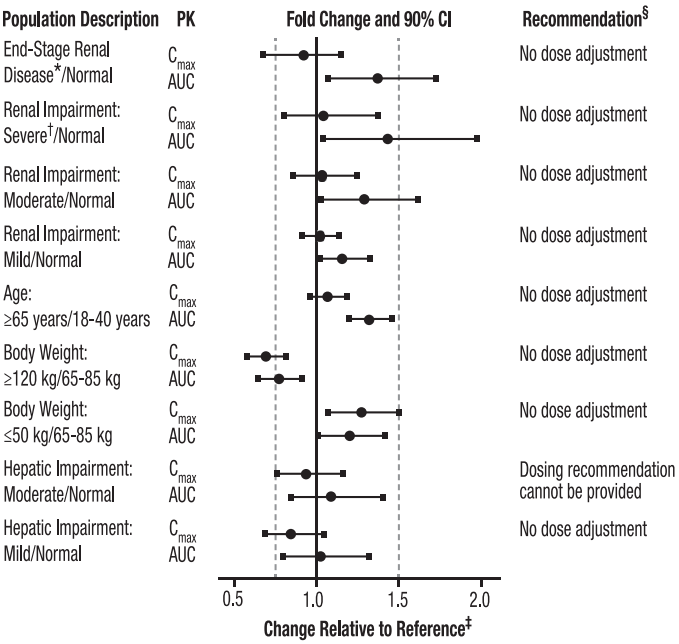
In dedicated studies conducted in healthy subjects, famotidine, atenolol, prasugrel, and enoxaparin did not meaningfully alter the pharmacokinetics of apixaban.

In studies conducted in healthy subjects, apixaban did not meaningfully alter the pharmacokinetics of digoxin, naproxen, atenolol, prasugrel, or acetylsalicylic acid.

Specific Populations

The effects of level of renal impairment, age, body weight, and level of hepatic impairment on the pharmacokinetics of apixaban are summarized in Figure 3.

Figure 3: Effect of Specific Populations on the Pharmacokinetics of Apixaban



* ESRD subjects treated with intermittent hemodialysis; reported PK findings are following single dose of apixaban post hemodialysis.

† Results reflect CrCl of 15 mL/min based on regression analysis.

‡ Dashed vertical lines illustrate pharmacokinetic changes that were used to inform dosing recommendations.

§ No dose adjustment is recommended for nonvalvular atrial fibrillation patients unless at least 2 of the following patient characteristics (age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL) are present.

Gender: A study in healthy subjects comparing the pharmacokinetics in males and females showed no meaningful difference.

Race: The results across pharmacokinetic studies in normal subjects showed no differences in apixaban pharmacokinetics among White/Caucasian, Asian, and Black/African American subjects. No dose adjustment is required based on race/ethnicity.

Hemodialysis in ESRD subjects: Systemic exposure to apixaban administered as a single 5 mg dose in ESRD subjects dosed immediately after the completion of a 4-hour hemodialysis session (post-dialysis) is 36% higher when compared to subjects with normal renal function (Figure 3).

The systemic exposure to apixaban administered 2 hours prior to a 4-hour hemodialysis session with a dialysate flow rate of 500 mL/min and a blood flow rate in the range of 350 to 500 mL/min is 17% higher compared to those with normal renal function. The dialysis clearance of apixaban is approximately 18 mL/min. The systemic exposure of apixaban is 14% lower on dialysis when compared to not on dialysis.

Protein binding was similar (92%-94%) between healthy controls and ESRD subjects during the on-dialysis and off-dialysis periods.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Apixaban was not carcinogenic when administered to mice and rats for up to 2 years. The systemic exposures (AUCs) of unbound apixaban in male and female mice at the highest doses tested (1500 and 3000 mg/kg/day) were 9 and 20 times, respectively, the human exposure of unbound drug at the MRHD of 10 mg/day. Systemic exposures of unbound apixaban in male and female rats at the highest dose tested (600 mg/kg/day) were 2 and 4 times, respectively, the human exposure.

Mutagenesis: Apixaban was neither mutagenic in the bacterial reverse mutation (Ames) assay, nor clastogenic in Chinese hamster ovary cells *in vitro*, in a 1-month *in vivo/in vitro* cytogenetics study in rat peripheral blood lymphocytes, or in a rat micronucleus study *in vivo*.

Impairment of Fertility: Apixaban had no effect on fertility in male or female rats when given at doses up to 600 mg/kg/day, a dose resulting in exposure levels that are 3 and 4 times, respectively, the human exposure.

Apixaban administered to female rats at doses up to 1000 mg/kg/day from implantation through the end of lactation produced no adverse findings in male offspring (F_1 generation) at doses up to 1000 mg/kg/day, a dose resulting in exposure that is 5 times the human exposure. Adverse effects in the F_1-generation female offspring were limited to decreased mating and fertility indices at 1000 mg/kg/day.

14 CLINICAL STUDIES

14.1 Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

ARISTOTLE

Evidence for the efficacy and safety of ELIQUIS was derived from ARISTOTLE, a multinational, double-blind study in patients with nonvalvular AF comparing the effects of ELIQUIS and warfarin on the risk of stroke and non-central nervous system (CNS) systemic embolism. In ARISTOTLE, patients were randomized to ELIQUIS 5 mg orally twice daily (or 2.5 mg twice daily in subjects with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL) or to warfarin (targeted to an INR range of 2.0–3.0). Patients had to have one or more of the following additional risk factors for stroke:

- prior stroke or transient ischemic attack (TIA)
- prior systemic embolism
- age ≥75 years
- arterial hypertension requiring treatment
- diabetes mellitus
- heart failure ≥New York Heart Association Class 2
- left ventricular ejection fraction ≤40%

The primary objective of ARISTOTLE was to determine whether ELIQUIS 5 mg twice daily (or 2.5 mg twice daily) was effective (noninferior to warfarin) in reducing the risk of stroke (ischemic or hemorrhagic) and systemic embolism. Superiority of ELIQUIS to warfarin was also examined for the primary endpoint (rate of stroke and systemic embolism), major bleeding, and death from any cause.

A total of 18,201 patients were randomized and followed on study treatment for a median of 89 weeks. Forty-three percent of patients were vitamin K antagonist (VKA) "naive," defined as having received ≤30 consecutive days of treatment with warfarin or another VKA before entering the study. The mean age was 69 years and the mean $CHADS_2$ score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk) was 2.1. The population was 65% male, 83% Caucasian, 14% Asian, and 1% Black. There was a history of stroke, TIA, or non-CNS systemic embolism in 19% of patients. Concomitant diseases of patients in this study included hypertension 88%,

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diabetes 25%, congestive heart failure (or left ventricular ejection fraction ≤40%) 35%, and prior myocardial infarction 14%. Patients treated with warfarin in ARISTOTLE had a mean percentage of time in therapeutic range (INR 2.0–3.0) of 62%.

ELIQUIS was superior to warfarin for the primary endpoint of reducing the risk of stroke and systemic embolism (Table 9 and Figure 4). Superiority to warfarin was primarily attributable to a reduction in hemorrhagic stroke and ischemic strokes with hemorrhagic conversion compared to warfarin. Purely ischemic strokes occurred with similar rates on both drugs.

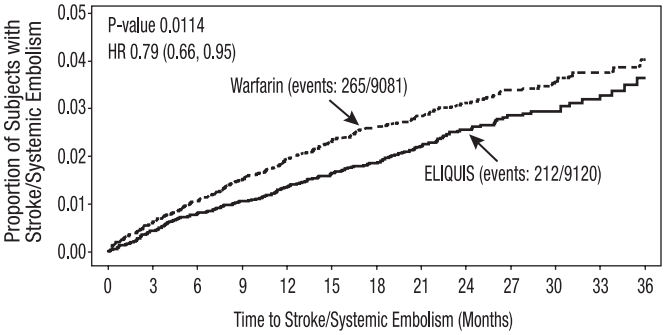
ELIQUIS also showed significantly fewer major bleeds than warfarin *[see Adverse Reactions (6.1)]*.

Table 9: Key Efficacy Outcomes in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE (Intent-to-Treat Analysis)

	ELIQUIS N=9120 n (%/year)	Warfarin N=9081 n (%/year)	Hazard Ratio (95% CI)	P-value
Stroke or systemic embolism	212 (1.27)	265 (1.60)	0.79 (0.66, 0.95)	0.01
Stroke	199 (1.19)	250 (1.51)	0.79 (0.65, 0.95)	
Ischemic without hemorrhage	140 (0.83)	136 (0.82)	1.02 (0.81, 1.29)	
Ischemic with hemorrhagic conversion	12 (0.07)	20 (0.12)	0.60 (0.29, 1.23)	
Hemorrhagic	40 (0.24)	78 (0.47)	0.51 (0.35, 0.75)	
Unknown	14 (0.08)	21 (0.13)	0.65 (0.33, 1.29)	
Systemic embolism	15 (0.09)	17 (0.10)	0.87 (0.44, 1.75)	

The primary endpoint was based on the time to first event (one per subject). Component counts are for subjects with any event, not necessarily the first.

Figure 4: Kaplan-Meier Estimate of Time to First Stroke or Systemic Embolism in ARISTOTLE (Intent-to-Treat Population)



Number of Subjects at Risk

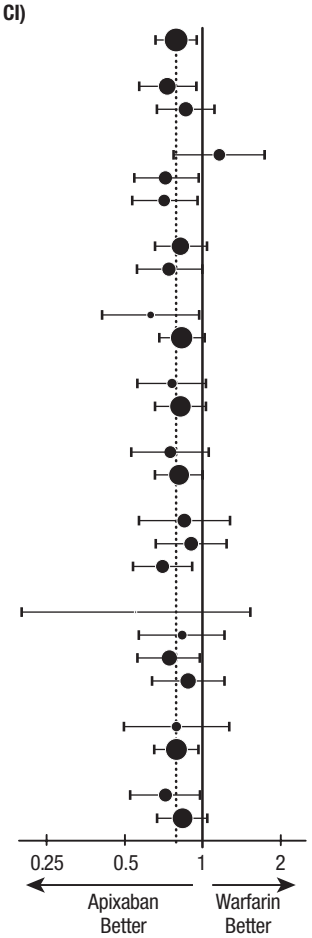
ELIQUIS	9120	8726	8440	6051	3464	1754	600
Warfarin	9081	8620	8301	5972	3405	1768	572

All-cause death was assessed using a sequential testing strategy that allowed testing for superiority if effects on earlier endpoints (stroke plus systemic embolus and major bleeding) were demonstrated. ELIQUIS treatment resulted in a significantly lower rate of all-cause death (p = 0.046) than did treatment with warfarin, primarily because of a reduction in cardiovascular death, particularly stroke deaths. Non-vascular death rates were similar in the treatment arms.

In ARISTOTLE, the results for the primary efficacy endpoint were generally consistent across most major subgroups including weight, $CHADS_2$ score (a scale from 0 to 6 used to predict risk of stroke in patients with AF, with higher scores predicting greater risk), prior warfarin use, level of renal impairment, geographic region, and aspirin use at randomization (Figure 5).

Figure 5: Stroke and Systemic Embolism Hazard Ratios by Baseline Characteristics – ARISTOTLE Study

	n of Events / N of Patients (% per year)		
Subgroup	**Apixaban**	**Warfarin**	**Hazard Ratio (95% CI)**
All Patients	212 / 9120 (1.3)	265 / 9081 (1.6)	0.79 (0.66, 0.95)
Prior Warfarin/VKA Status			
Experienced (57%)	102 / 5208 (1.1)	138 / 5193 (1.5)	0.73 (0.57, 0.95)
Naive (43%)	110 / 3912 (1.5)	127 / 3888 (1.8)	0.86 (0.66, 1.11)
Age			
<65 (30%)	51 / 2731 (1.0)	44 / 2740 (0.9)	1.16 (0.77, 1.73)
≥65 and <75 (39%)	82 / 3539 (1.3)	112 / 3513 (1.7)	0.72 (0.54, 0.96)
≥75 (31%)	79 / 2850 (1.6)	109 / 2828 (2.2)	0.71 (0.53, 0.95)
Sex			
Male (65%)	132 / 5886 (1.2)	160 / 5899 (1.5)	0.82 (0.65, 1.04)
Female (35%)	80 / 3234 (1.3)	105 / 3182 (1.8)	0.74 (0.56, 1.00)
Weight			
≤60 kg (11%)	34 / 1018 (2.0)	52 / 967 (3.2)	0.63 (0.41, 0.97)
>60 kg (89%)	177 / 8070 (1.2)	212 / 8084 (1.4)	0.83 (0.68, 1.01)
Prior Stroke or TIA			
Yes (19%)	73 / 1694 (2.5)	98 / 1742 (3.2)	0.76 (0.56, 1.03)
No (81%)	139 / 7426 (1.0)	167 / 7339 (1.2)	0.82 (0.65, 1.03)
Diabetes Mellitus			
Yes (25%)	57 / 2284 (1.4)	75 / 2263 (1.9)	0.75 (0.53, 1.05)
No (75%)	155 / 6836 (1.2)	190 / 6818 (1.5)	0.81 (0.65, 1.00)
$CHADS_2$ Score			
≤1 (34%)	44 / 3100 (0.7)	51 / 3083 (0.9)	0.85 (0.57, 1.27)
2 (36%)	74 / 3262 (1.2)	82 / 3254 (1.4)	0.90 (0.66, 1.23)
≥3 (30%)	94 / 2758 (2.0)	132 / 2744 (2.8)	0.70 (0.54, 0.91)
Creatinine Clearance			
<30 mL/min (1%)	6 / 137 (2.8)	10 / 133 (5.1)	0.55 (0.20, 1.53)
30-50 mL/min (15%)	48 / 1365 (2.0)	59 / 1382 (2.5)	0.83 (0.57, 1.21)
>50-80 mL/min (42%)	87 / 3817 (1.2)	116 / 3770 (1.7)	0.74 (0.56, 0.97)
>80 mL/min (41%)	70 / 3761 (1.0)	79 / 3757 (1.1)	0.88 (0.64, 1.21)
Geographic Region			
US (19%)	31 / 1720 (0.9)	39 / 1697 (1.2)	0.79 (0.50, 1.27)
Non-US (81%)	181 / 7400 (1.3)	226 / 7384 (1.7)	0.79 (0.65, 0.96)
Aspirin at Randomization			
Yes (31%)	70 / 2859 (1.3)	94 / 2773 (1.9)	0.72 (0.53, 0.98)
No (69%)	142 / 6261 (1.2)	171 / 6308 (1.5)	0.83 (0.67, 1.04)



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were pre-specified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

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At the end of the ARISTOTLE study, warfarin patients who completed the study were generally maintained on a VKA with no interruption of anticoagulation. ELIQUIS patients who completed the study were generally switched to a VKA with a 2-day period of coadministration of ELIQUIS and VKA, so that some patients may not have been adequately anticoagulated after stopping ELIQUIS until attaining a stable and therapeutic INR. During the 30 days following the end of the study, there were 21 stroke or systemic embolism events in the 6791 patients (0.3%) in the ELIQUIS arm compared to 5 in the 6569 patients (0.1%) in the warfarin arm *[see Dosage and Administration (2.4)]*.

AVERROES

In AVERROES, patients with nonvalvular atrial fibrillation thought not to be candidates for warfarin therapy were randomized to treatment with ELIQUIS 5 mg orally twice daily (or 2.5 mg twice daily in selected patients) or aspirin 81 to 324 mg once daily. The primary objective of the study was to determine if ELIQUIS was superior to aspirin for preventing the composite outcome of stroke or systemic embolism. AVERROES was stopped early on the basis of a prespecified interim analysis showing a significant reduction in stroke and systemic embolism for ELIQUIS compared to aspirin that was associated with a modest increase in major bleeding (Table 10) *[see Adverse Reactions (6.1)]*.

Table 10: Key Efficacy Outcomes in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	ELIQUIS N=2807 n (%/year)	Aspirin N=2791 n (%/year)	Hazard Ratio (95% CI)	P-value
Stroke or systemic embolism	51 (1.62)	113 (3.63)	0.45 (0.32, 0.62)	<0.0001
Stroke				
Ischemic or undetermined	43 (1.37)	97 (3.11)	0.44 (0.31, 0.63)	-
Hemorrhagic	6 (0.19)	9 (0.28)	0.67 (0.24, 1.88)	-
Systemic embolism	2 (0.06)	13 (0.41)	0.15 (0.03, 0.68)	-
MI	24 (0.76)	28 (0.89)	0.86 (0.50, 1.48)	-
All-cause death	111 (3.51)	140 (4.42)	0.79 (0.62, 1.02)	0.068
Vascular death	84 (2.65)	96 (3.03)	0.87 (0.65, 1.17)	-

14.2 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The clinical evidence for the effectiveness of ELIQUIS is derived from the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical trials in adult patients undergoing elective hip (ADVANCE-3) or knee (ADVANCE-2 and ADVANCE-1) replacement surgery. A total of 11,659 patients were randomized in 3 double-blind, multi-national studies. Included in this total were 1866 patients age 75 or older, 1161 patients with low body weight (≤60 kg), 2528 patients with Body Mass Index ≥33 kg/m^2, and 625 patients with severe or moderate renal impairment.

In the ADVANCE-3 study, 5407 patients undergoing elective hip replacement surgery were randomized to receive either ELIQUIS 2.5 mg orally twice daily or enoxaparin 40 mg subcutaneously once daily. The first dose of ELIQUIS was given 12 to 24 hours post surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. Treatment duration was 32 to 38 days.

In patients undergoing elective knee replacement surgery, ELIQUIS 2.5 mg orally twice daily was compared to enoxaparin 40 mg subcutaneously once daily (ADVANCE-2, N=3057) or enoxaparin 30 mg subcutaneously every 12 hours (ADVANCE-1, N=3195). In the ADVANCE-2 study, the first dose of ELIQUIS was given 12 to 24 hours post surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. In the ADVANCE-1 study, both ELIQUIS and enoxaparin were initiated 12 to 24 hours post surgery. Treatment duration in both ADVANCE-2 and ADVANCE-1 was 10 to 14 days.

In all 3 studies, the primary endpoint was a composite of adjudicated asymptomatic and symptomatic DVT, nonfatal PE, and all-cause death at the end of the double-blind intended treatment period. In ADVANCE-3 and ADVANCE-2, the primary endpoint was tested for noninferiority, then superiority, of ELIQUIS to enoxaparin. In ADVANCE-1, the primary endpoint was tested for noninferiority of ELIQUIS to enoxaparin.

The efficacy data are provided in Tables 11 and 12.

Table 11: Summary of Key Efficacy Analysis Results During the Intended Treatment Period for Patients Undergoing Elective Hip Replacement Surgery*

	ADVANCE-3		
Events During 35-Day Treatment Period	ELIQUIS 2.5 mg po bid	Enoxaparin 40 mg sc qd	Relative Risk (95% CI) P-value
Number of Patients	**N=1949**	**N=1917**	
Total VTE†/All-cause death	27 (1.39%) (0.95, 2.02)	74 (3.86%) (3.08, 4.83)	0.36 (0.22, 0.54) p<0.0001
Number of Patients	**N=2708**	**N=2699**	
All-cause death	3 (0.11%) (0.02, 0.35)	1 (0.04%) (0.00, 0.24)	
PE	3 (0.11%) (0.02, 0.35)	5 (0.19%) (0.07, 0.45)	
Symptomatic DVT	1 (0.04%) (0.00, 0.24)	5 (0.19%) (0.07, 0.45)	
Number of Patients	**N=2196**	**N=2190**	
Proximal DVT‡	7 (0.32%) (0.14, 0.68)	20 (0.91%) (0.59, 1.42)	
Number of Patients	**N=1951**	**N=1908**	
Distal DVT‡	20 (1.03%) (0.66, 1.59)	57 (2.99%) (2.31, 3.86)	

*Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints.

†Total VTE includes symptomatic and asymptomatic DVT and PE.

‡Includes symptomatic and asymptomatic DVT.

Table 12: Summary of Key Efficacy Analysis Results During the Intended Treatment Period for Patients Undergoing Elective Knee Replacement Surgery*

	ADVANCE-1			ADVANCE-2		
Events during 12-day treatment period	ELIQUIS 2.5 mg po bid	Enoxaparin 30 mg sc q12h	Relative Risk (95% CI) P-value	ELIQUIS 2.5 mg po bid	Enoxaparin 40 mg sc qd	Relative Risk (95% CI) P-value
Number of Patients	**N=1157**	**N=1130**		**N=976**	**N=997**	
Total VTE†/All-cause death	104 (8.99%) (7.47, 10.79)	100 (8.85%) (7.33, 10.66)	1.02 (0.78, 1.32) NS	147 (15.06%) (12.95, 17.46)	243 (24.37%) (21.81, 27.14)	0.62 (0.51, 0.74) p<0.0001
Number of Patients	**N=1599**	**N=1596**		**N=1528**	**N=1529**	
All-cause death	3 (0.19%) (0.04, 0.59)	3 (0.19%) (0.04, 0.59)		2 (0.13%) (0.01, 0.52)	0 (0%) (0.00, 0.31)	
PE	16 (1.0%) (0.61, 1.64)	7 (0.44%) (0.20, 0.93)		4 (0.26%) (0.08, 0.70)	0 (0%) (0.00, 0.31)	
Symptomatic DVT	3 (0.19%) (0.04, 0.59)	7 (0.44%) (0.20, 0.93)		3 (0.20%) (0.04, 0.61)	7 (0.46%) (0.20, 0.97)	
Number of Patients	**N=1254**	**N=1207**		**N=1192**	**N=1199**	
Proximal DVT‡	9 (0.72%) (0.36, 1.39)	11 (0.91%) (0.49, 1.65)		9 (0.76%) (0.38, 1.46)	26 (2.17%) (1.47, 3.18)	
Number of Patients	**N=1146**	**N=1133**		**N=978**	**N=1000**	
Distal DVT‡	83 (7.24%) (5.88, 8.91)	91 (8.03%) (6.58, 9.78)		142 (14.52%) (12.45, 16.88)	239 (23.9%) (21.36, 26.65)	

* Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints.

† Total VTE includes symptomatic and asymptomatic DVT and PE.

‡ Includes symptomatic and asymptomatic DVT.

The efficacy profile of ELIQUIS was generally consistent across subgroups of interest for this indication (e.g., age, gender, race, body weight, renal impairment).

14.3 Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT and PE

Efficacy and safety of ELIQUIS for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following 6 to 12 months of anticoagulant treatment was derived from the AMPLIFY and AMPLIFY-EXT studies. Both studies were randomized, parallel-group, double-blind trials in patients with symptomatic proximal DVT and/or symptomatic PE. All key safety and efficacy endpoints were adjudicated in a blinded manner by an independent committee.

AMPLIFY

The primary objective of AMPLIFY was to determine whether ELIQUIS was noninferior to enoxaparin/warfarin for the incidence of recurrent VTE (venous thromboembolism) or VTE-related death. Patients with an objectively confirmed symptomatic DVT and/or PE were randomized to treatment with ELIQUIS 10 mg twice daily orally for 7 days followed by ELIQUIS 5 mg twice daily orally for 6 months, or enoxaparin 1 mg/kg twice daily subcutaneously for at least 5 days (until INR ≥2) followed by warfarin (target INR range 2.0-3.0) orally for 6 months. Patients who required thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent, and patients with creatinine clearance <25 mL/min, significant liver disease, an existing heart valve or atrial fibrillation, or active bleeding were excluded from the AMPLIFY study. Patients were allowed to enter the study with or without prior parenteral anticoagulation (up to 48 hours).

A total of 5244 patients were evaluable for efficacy and were followed for a mean of 154 days in the ELIQUIS group and 152 days in the enoxaparin/warfarin group. The mean age was 57 years. The AMPLIFY study population was 59% male, 83% Caucasian, 8% Asian, and 4% Black. For patients randomized to warfarin, the mean percentage of time in therapeutic range (INR 2.0-3.0) was 60.9%.

Approximately 90% of patients enrolled in AMPLIFY had an unprovoked DVT or PE at baseline. The remaining 10% of patients with a provoked DVT or PE were required to have an additional ongoing risk factor in order to be randomized, which included previous episode of DVT or PE, immobilization, history of cancer, active cancer, and known prothrombotic genotype.

ELIQUIS was shown to be noninferior to enoxaparin/warfarin in the AMPLIFY study for the primary endpoint of recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) or VTE-related death over 6 months of therapy (Table 13).

Table 13: Efficacy Results in the AMPLIFY Study

	ELIQUIS N=2609 n	Enoxaparin/Warfarin N=2635 n	Relative Risk (95% CI)
VTE or VTE-related death*	59 (2.3%)	71 (2.7%)	0.84 (0.60, 1.18)
DVT†	22 (0.8%)	35 (1.3%)	
PE†	27 (1.0%)	25 (0.9%)	
VTE-related death†	12 (0.4%)	16 (0.6%)	
VTE or all-cause death	84 (3.2%)	104 (4.0%)	0.82 (0.61, 1.08)
VTE or CV-related death	61 (2.3%)	77 (2.9%)	0.80 (0.57, 1.11)

* Noninferior compared to enoxaparin/warfarin (P-value <0.0001).

† Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

In the AMPLIFY study, patients were stratified according to their index event of PE (with or without DVT) or DVT (without PE). Efficacy in the initial treatment of VTE was consistent between the two subgroups.

AMPLIFY-EXT

Patients who had been treated for DVT and/or PE for 6 to 12 months with anticoagulant therapy without having a recurrent event were randomized to treatment with ELIQUIS 2.5 mg orally twice daily, ELIQUIS 5 mg orally twice daily, or placebo for 12 months. Approximately one-third of patients participated in the AMPLIFY study prior to enrollment in the AMPLIFY-EXT study.

A total of 2482 patients were randomized to study treatment and were followed for a mean of approximately 330 days in the ELIQUIS group and 312 days in the placebo group. The mean age in the AMPLIFY-EXT study was 57 years. The study population was 57% male, 85% Caucasian, 5% Asian, and 3% Black.

The AMPLIFY-EXT study enrolled patients with either an unprovoked DVT or PE at baseline (approximately 92%) or patients with a provoked baseline event and one additional risk factor for recurrence (approximately 8%). However, patients who had experienced multiple episodes of unprovoked DVT or PE were excluded from the AMPLIFY-EXT study. In the AMPLIFY-EXT study, both doses of ELIQUIS were superior to placebo in the primary endpoint of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE), or all-cause death (Table 14).

ELIQUIS® (apixaban)

Table 14: Efficacy Results in the AMPLIFY-EXT Study

				Relative Risk (95% CI)	
	ELIQUIS 2.5 mg bid N=840	ELIQUIS 5 mg bid N=813	Placebo N=829	ELIQUIS 2.5 mg bid vs Placebo	ELIQUIS 5 mg bid vs Placebo
	n (%)				
Recurrent VTE or all-cause death	32 (3.8)	34 (4.2)	96 (11.6)	0.33 (0.22, 0.48) p<0.0001	0.36 (0.25, 0.53) p<0.0001
DVT*	19 (2.3)	28 (3.4)	72 (8.7)		
PE*	23 (2.7)	25 (3.1)	37 (4.5)		
All-cause death	22 (2.6)	25 (3.1)	33 (4.0)		

*Patients with more than one event are counted in multiple rows.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ELIQUIS (apixaban) tablets are available as listed in the table below.

Tablet Strength	Tablet Color/Shape	Tablet Markings	Package Size	NDC Code
2.5 mg	Yellow, round, biconvex	Debossed with "893" on one side and "2½" on the other side	Bottles of 60 Bottles of 180 Hospital Unit-Dose Blister Package of 100	0003-0893-21 0003-0893-41 0003-0893-31
5 mg	Pink, oval, biconvex	Debossed with "894" on one side and "5" on the other side	Bottles of 60 Bottles of 180 Hospital Unit-Dose Blister Package of 100	0003-0894-21 0003-0894-41 0003-0894-31

Storage and Handling

Store at 20°C to 25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

- Not to discontinue ELIQUIS without talking to their physician first.
- That it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- To tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas *[see Warnings and Precautions (5.3)]*. If any of these symptoms occur, advise the patient to seek emergent medical attention.
- To tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS *[see Use in Specific Populations (8.1, 8.3)]*.
- How to take ELIQUIS if they cannot swallow, or require a nasogastric tube *[see Dosage and Administration (2.6)]*.
- What to do if a dose is missed *[see Dosage and Administration (2.2)]*.

Marketed by:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA
and
Pfizer Inc
New York, New York 10017 USA

1356615A2 / 1356514A1

MEDICATION GUIDE

ELIQUIS® (ELL eh kwiss)
(apixaban)
tablets

What is the most important information I should know about ELIQUIS?

- **For people taking ELIQUIS for atrial fibrillation:**

  People with atrial fibrillation (a type of irregular heartbeat) are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. ELIQUIS lowers your chance of having a stroke by helping to prevent clots from forming. If you stop taking ELIQUIS, you may have increased risk of forming a clot in your blood.

  Do not stop taking ELIQUIS without talking to the doctor who prescribes it for you. Stopping ELIQUIS increases your risk of having a stroke.

  ELIQUIS may need to be stopped, if possible, prior to surgery or a medical or dental procedure. Ask the doctor who prescribed ELIQUIS for you when you should stop taking it. Your doctor will tell you when you may start taking ELIQUIS again after your surgery or procedure. If you have to stop taking ELIQUIS, your doctor may prescribe another medicine to help prevent a blood clot from forming.

- **ELIQUIS can cause bleeding** which can be serious and rarely may lead to death. This is because ELIQUIS is a blood thinner medicine that reduces blood clotting.

  You may have a higher risk of bleeding if you take ELIQUIS and take other medicines that increase your risk of bleeding, including:

  - aspirin or aspirin-containing products
  - long-term (chronic) use of nonsteroidal anti-inflammatory drugs (NSAIDs)
  - warfarin sodium (COUMADIN®, JANTOVEN®)
  - any medicine that contains heparin
  - selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)
  - other medicines to help prevent or treat blood clots

  Tell your doctor if you take any of these medicines. Ask your doctor or pharmacist if you are not sure if your medicine is one listed above.

  While taking ELIQUIS:

  - you may bruise more easily
  - it may take longer than usual for any bleeding to stop

  Call your doctor or get medical help right away if you have any of these signs or symptoms of bleeding when taking ELIQUIS:

  - unexpected bleeding, or bleeding that lasts a long time, such as:
    - unusual bleeding from the gums
    - nosebleeds that happen often
    - menstrual bleeding or vaginal bleeding that is heavier than normal
  - bleeding that is severe or you cannot control
  - red, pink, or brown urine
  - red or black stools (looks like tar)

- cough up blood or blood clots
- vomit blood or your vomit looks like coffee grounds
- unexpected pain, swelling, or joint pain
- headaches, feeling dizzy or weak

- **ELIQUIS is not for patients with artificial heart valves.**
- **Spinal or epidural blood clots (hematoma).** People who take a blood thinner medicine (anticoagulant) like ELIQUIS, and have medicine injected into their spinal and epidural area, or have a spinal puncture have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your risk of developing a spinal or epidural blood clot is higher if:
  - a thin tube called an epidural catheter is placed in your back to give you certain medicine
  - you take NSAIDs or a medicine to prevent blood from clotting
  - you have a history of difficult or repeated epidural or spinal punctures
  - you have a history of problems with your spine or have had surgery on your spine

  If you take ELIQUIS and receive spinal anesthesia or have a spinal puncture, your doctor should watch you closely for symptoms of spinal or epidural blood clots or bleeding. Tell your doctor right away if you have tingling, numbness, or muscle weakness, especially in your legs and feet.

What is ELIQUIS?

ELIQUIS is a prescription medicine used to:

- reduce the risk of stroke and blood clots in people who have atrial fibrillation.
- reduce the risk of forming a blood clot in the legs and lungs of people who have just had hip or knee replacement surgery.
- treat blood clots in the veins of your legs (deep vein thrombosis) or lungs (pulmonary embolism), and reduce the risk of them occurring again.

It is not known if ELIQUIS is safe and effective in children.

Who should not take ELIQUIS?

Do not take ELIQUIS if you:

- currently have certain types of abnormal bleeding.
- have had a serious allergic reaction to ELIQUIS. Ask your doctor if you are not sure.

What should I tell my doctor before taking ELIQUIS?

Before you take ELIQUIS, tell your doctor if you:

- have kidney or liver problems
- have any other medical condition
- have ever had bleeding problems
- are pregnant or plan to become pregnant. It is not known if ELIQUIS will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ELIQUIS passes into your breast milk. You and your doctor should decide if you will take ELIQUIS or breastfeed. You should not do both.

Tell all of your doctors and dentists that you are taking ELIQUIS. They should talk to the doctor who prescribed ELIQUIS for you, before you have **any** surgery, medical or dental procedure.

ELIQUIS® (apixaban)

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some of your other medicines may affect the way ELIQUIS works. Certain medicines may increase your risk of bleeding or stroke when taken with ELIQUIS. See "**What is the most important information I should know about ELIQUIS?**"

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take ELIQUIS?

- **Take ELIQUIS exactly as prescribed by your doctor.**
- Take ELIQUIS twice every day with or without food.
- Do not change your dose or stop taking ELIQUIS unless your doctor tells you to.
- If you miss a dose of ELIQUIS, take it as soon as you remember. Do not take more than one dose of ELIQUIS at the same time to make up for a missed dose.
- If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take ELIQUIS.
- Your doctor will decide how long you should take ELIQUIS. **Do not stop taking it without first talking with your doctor. If you are taking ELIQUIS for atrial fibrillation, stopping ELIQUIS may increase your risk of having a stroke.**
- **Do not run out of ELIQUIS. Refill your prescription before you run out.** When leaving the hospital following hip or knee replacement, be sure that you will have ELIQUIS available to avoid missing any doses.
- If you take too much ELIQUIS, call your doctor or go to the nearest hospital emergency room right away.
- Call your doctor or healthcare provider right away if you fall or injure yourself, especially if you hit your head. Your doctor or healthcare provider may need to check you.

What are the possible side effects of ELIQUIS?

- See "**What is the most important information I should know about ELIQUIS?**"
- ELIQUIS can cause a skin rash or severe allergic reaction. Call your doctor or get medical help right away if you have any of the following symptoms:
    - chest pain or tightness
    - swelling of your face or tongue
    - trouble breathing or wheezing
    - feeling dizzy or faint

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of ELIQUIS. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ELIQUIS?

Store ELIQUIS at room temperature between 68°F to 77°F (20°C to 25°C).

Keep ELIQUIS and all medicines out of the reach of children.

General Information about ELIQUIS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ELIQUIS for a condition for which it was not prescribed. Do not give ELIQUIS to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about ELIQUIS that is written for health professionals.

For more information, call 1-855-354-7847 (1-855-ELIQUIS) or go to www.ELIQUIS.com.

What are the ingredients in ELIQUIS?

Active ingredient: apixaban.

Inactive ingredients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate. The film coating contains lactose monohydrate, hypromellose, titanium dioxide, triacetin, and yellow iron oxide (2.5 mg tablets) or red iron oxide (5 mg tablets).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Marketed by:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA
and
Pfizer Inc
New York, New York 10017 USA

1356615A2 / 1356514A1
1356616A0 Revised July 2016

432US1603587-11-01

APPENDIX E. US PACKAGE INSERT FOR EDOXABAN (SAVAYSA)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SAVAYSA™ safely and effectively. See full prescribing information for SAVAYSA.

SAVAYSA (edoxaban) tablets, for oral use
Initial U.S. Approval: 2015

WARNING (A) REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CREATININE CLEARANCE (CRCL) > 95 ML/MIN (B) PREMATURE DISCONTINUATION OF SAVAYSA INCREASES THE RISK OF ISCHEMIC EVENTS (C) SPINAL/EPIDURAL HEMATOMA

See full prescribing information for complete boxed warning.

(A) REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CRCL > 95 ML/MIN: SAVAYSA should not be used in patients with CrCL > 95 mL/min. In the ENGAGE AF-TIMI 48 study, nonvalvular atrial fibrillation patients with CrCL > 95 mL/min had an increased rate of ischemic stroke with SAVAYSA 60 mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used (5.1).

(B) PREMATURE DISCONTINUATION OF SAVAYSA INCREASES THE RISK OF ISCHEMIC EVENTS: Premature discontinuation of any oral anticoagulant in the absence of adequate alternative anticoagulation increases the risk of ischemic events. If SAVAYSA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant as described in the transition guidance (2.4, 5.2, 14).

(C) SPINAL/EPIDURAL HEMATOMA: Epidural or spinal hematomas may occur in patients treated with SAVAYSA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures (5.4).

RECENT MAJOR CHANGES

Warnings and Precautions (5.3) 9/2016

INDICATIONS AND USAGE

SAVAYSA is a factor Xa inhibitor indicated:
To reduce the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF) (1.1)

- *Limitation of Use for NVAF*
  SAVAYSA should not be used in patients with creatinine clearance (CrCL) > 95 mL/min because of increased risk of ischemic stroke compared to warfarin at the highest dose studied (60 mg) (1.1)

SAVAYSA is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant (1.2)

DOSAGE AND ADMINISTRATION

- Treatment of NVAF:
  Assess CrCL before initiating therapy (2.1)
  The recommended dose is 60 mg once daily in patients with CrCL >50 to ≤ 95 mL/min. Do not use SAVAYSA in patients with CrCL > 95 mL/min (2.1)
  Reduce dose to 30 mg once daily in patients with creatinine clearance 15 to 50 mL/min (2.1)
- Treatment of DVT and PE:
  The recommended dose is 60 mg once daily (2.2)
  The recommended dose is 30 mg once daily for patients with CrCL 15 to 50 mL/min or body weight less than or equal to 60 kg or who use certain P-gp inhibitors (2.2)

DOSAGE FORMS AND STRENGTHS

- Tablets: 60 mg, 30 mg, and 15 mg (3)

CONTRAINDICATIONS

- Active pathological bleeding (4)

WARNINGS AND PRECAUTIONS

- Bleeding: Serious and potentially fatal bleeding. Promptly evaluate signs and symptoms of blood loss (5.2)
- Mechanical heart valves or moderate to severe mitral stenosis: Use is not recommended (5.5)

ADVERSE REACTIONS

Treatment of NVAF: The most common adverse reactions (≥ 5%) are bleeding and anemia (6.1)
Treatment of DVT and PE: The most common adverse reactions (≥ 1%) are bleeding, rash, abnormal liver function tests and anemia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Anticoagulants: Avoid concomitant use (7.1)
- Rifampin: Avoid concomitant use (7.2)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Discontinue drug or discontinue nursing (8.3)
- Impaired renal function (CrCL 15 to 50 mL/min): Reduce dose (2.1, 2.2, 8.6)
- Moderate or severe hepatic impairment: Not recommended (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING (A) REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CREATININE CLEARANCE (CRCL) > 95 ML/MIN (B) PREMATURE DISCONTINUATION OF SAVAYSA INCREASES THE RISK OF ISCHEMIC EVENTS (C) SPINAL/EPIDURAL HEMATOMA

A. REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CRCL > 95 ML/MIN

SAVAYSA should not be used in patients with CrCL > 95 mL/min. In the ENGAGE AF-TIMI 48 study, nonvalvular atrial fibrillation patients with CrCL > 95 mL/min had an increased rate of ischemic stroke with SAVAYSA 60 mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used *[see Dosage and Administration (2.1), Warnings and Precautions (5.1), and Clinical Studies (14.1)]*.

B. PREMATURE DISCONTINUATION OF SAVAYSA INCREASES THE RISK OF ISCHEMIC EVENTS

Premature discontinuation of any oral anticoagulant in the absence of adequate alternative anticoagulation increases the risk of ischemic events. If SAVAYSA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant as described in the transition guidance *[see Dosage and Administration (2.4), Warnings and Precautions (5.2), and Clinical Studies (14.1)]*.

C. SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with SAVAYSA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of SAVAYSA and neuraxial procedures is not known**

***[see Warnings and Precautions (5.4)]*.**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions (5.4)]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated *[see Warnings and Precautions (5.4)]*.

1 INDICATIONS AND USAGE

1.1 Reduction in the Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

SAVAYSA is indicated to reduce the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF).

Limitation of Use for NVAF

SAVAYSA should not be used in patients with CrCL > 95 mL/min because of an increased risk of ischemic stroke compared to warfarin *[see Dosage and Administration (2.1), Warnings and Precautions (5.1), Clinical Studies (14.1)]*.

1.2 Treatment of Deep Vein Thrombosis and Pulmonary Embolism

SAVAYSA is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant.

2 DOSAGE AND ADMINISTRATION

2.1 Nonvalvular Atrial Fibrillation

The recommended dose of SAVAYSA is 60 mg taken orally once daily *[see Warnings and Precautions (5.1), Clinical Studies (14.1)]*. Assess creatinine clearance, as calculated using the Cockcroft-Gault equation*, before initiating therapy with SAVAYSA. Do not use SAVAYSA in patients with CrCL > 95 mL/min.

Reduce SAVAYSA dose to 30 mg once daily in patients with CrCL 15 to 50 mL/min *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

*Cockcroft-Gault CrCL = (140-age) x (weight in kg) x (0.85 if female) / (72 x creatinine in mg/dL).

2.2 Treatment of Deep Vein Thrombosis and Pulmonary Embolism

The recommended dose of SAVAYSA is 30 mg once daily in patients with CrCL 15 to 50 mL/min, patients who weigh less than or equal to 60 kg, or patients who are taking certain concomitant P-gp inhibitor medications based on clinical study data in this indication *[see Clinical Studies (14.2)]*.

2.3 Administration Information

If a dose of SAVAYSA is missed, the dose should be taken as soon as possible on the same day. Dosing should resume the next day according to the normal dosing schedule. The dose should not be doubled to make up for a missed dose.

SAVAYSA can be taken without regard to food *[see Clinical Pharmacology (12.3)]*.

2.4 Transition to or from SAVAYSA

Transition to SAVAYSA

From	To	Recommendation
Warfarin or other Vitamin K Antagonists	SAVAYSA	Discontinue warfarin and start SAVAYSA when the INR is ≤ 2.5
Oral anticoagulants other than warfarin or other Vitamin K Antagonists	SAVAYSA	Discontinue current oral anticoagulant and start SAVAYSA at the time of the next scheduled dose of the other oral anticoagulant
Low Molecular Weight Heparin (LMWH)	SAVAYSA	Discontinue LMWH and start SAVAYSA at the time of the next scheduled administration of LMWH
Unfractionated heparin	SAVAYSA	Discontinue the infusion and start SAVAYSA 4 hours later

Transition from SAVAYSA

From	To	Recommendation
SAVAYSA	Warfarin	*Oral option:* For patients taking 60 mg of SAVAYSA, reduce the dose to 30 mg and begin warfarin concomitantly. For patients receiving 30 mg of SAVAYSA, reduce the dose to 15 mg and begin warfarin concomitantly. INR must be measured at least weekly and just prior to the daily dose of SAVAYSA to minimize the influence of SAVAYSA on INR measurements. Once a stable INR ≥ 2.0 is achieved, SAVAYSA should be discontinued and the warfarin continued
SAVAYSA	Warfarin	*Parenteral option:* Discontinue SAVAYSA and administer a parenteral anticoagulant and warfarin at the time of the next scheduled SAVAYSA dose. Once a stable INR ≥ 2.0 is achieved the parenteral anticoagulant should be discontinued and the warfarin continued
SAVAYSA	Non-Vitamin-K-Dependent Oral anticoagulants	Discontinue SAVAYSA and start the other oral anticoagulant at the time of the next dose of SAVAYSA
SAVAYSA	Parenteral anticoagulants	Discontinue SAVAYSA and start the parenteral anticoagulant at the time of the next dose of SAVAYSA

Abbreviations: INR=International Normalized Ratio

2.5 Discontinuation for Surgery and Other Interventions

Discontinue SAVAYSA at least 24 hours before invasive or surgical procedures because of the risk of bleeding *[see Warnings and Precautions (5.3)]*.

If surgery cannot be delayed, there is an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention *[see Warnings and Precautions (5.3)]*.

SAVAYSA can be restarted after the surgical or other procedure as soon as adequate hemostasis has been established noting that the time to onset of pharmacodynamic effect is 1-2 hours *[see Warnings and Precautions (5.2)]*. Administer a parenteral anticoagulant and then switch to oral SAVAYSA, if oral medication cannot be taken during or after surgical intervention.

3 DOSAGE FORMS AND STRENGTHS

- 60 mg, yellow round shaped, film-coated tablets, debossed with DSC L60 on one side
- 30 mg, pink round shaped, film-coated tablets, debossed with DSC L30 on one side
- 15 mg, orange round shaped, film-coated tablets, debossed with DSC L15 on one side

4 CONTRAINDICATIONS

SAVAYSA is contraindicated in patients with:

- Active pathological bleeding *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Reduced Efficacy in Nonvalvular Atrial Fibrillation Patients with CrCL > 95 mL/min

SAVAYSA should not be used in patients with CrCL > 95 mL/min. In the randomized ENGAGE AF-TIMI 48 study, NVAF patients with CrCL > 95 mL/min had an increased rate of ischemic stroke with SAVAYSA 60 mg daily compared to patients treated with warfarin. In these patients another anticoagulant should be used *[see Dosage and Administration (2.1)*, *Clinical Studies (14.1)]*.

5.2 Increased Risk of Stroke with Discontinuation of SAVAYSA in Patients with Nonvalvular Atrial Fibrillation

Premature discontinuation of any oral anticoagulant in the absence of adequate alternative anticoagulation increases the risk of ischemic events. If SAVAYSA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant as described in the transition guidance *[see Dosage and Administration (2.4) and Clinical Studies (14.1)]*.

5.3 Risk of Bleeding

SAVAYSA increases the risk of bleeding and can cause serious and potentially fatal bleeding. Promptly evaluate any signs or symptoms of blood loss.

Discontinue SAVAYSA in patients with active pathological bleeding.

Concomitant use of drugs affecting hemostasis may increase the risk of bleeding. These include aspirin and other antiplatelet agents, other antithrombotic agents, fibrinolytic therapy, chronic use of nonsteroidal antiinflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors *[see Drug Interactions (7.1)]*.

Reversal of Anticoagulant Effect

There is no established way to reverse the anticoagulant effects of SAVAYSA, which can be expected to persist for approximately 24 hours after the last dose. The anticoagulant effect of SAVAYSA cannot be reliably monitored with standard laboratory testing. A specific reversal agent for edoxaban is not available. Hemodialysis does not significantly contribute to edoxaban clearance *[see Clinical Pharmacology (12.3)]*. Protamine sulfate, vitamin K, and tranexamic acid are not expected to reverse the anticoagulant activity of SAVAYSA. The use of prothrombin complex concentrates (PCC), or other procoagulant reversal agents such as activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (rFVIIa) may be considered but has not been evaluated in clinical outcome studies *[see Clinical Pharmacology (12.2)]*. When PCCs are used, monitoring for anticoagulation effect of edoxaban using clotting test (PT, INR, or aPTT) or anti-FXa activity is not useful and is not recommended.

5.4 Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 12 hours after the last administration of SAVAYSA. The next dose of SAVAYSA should not be administered earlier than 2 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel, or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

5.5 Patients with Mechanical Heart Valves or Moderate to Severe Mitral Stenosis

The safety and efficacy of SAVAYSA has not been studied in patients with mechanical heart valves or moderate to severe mitral stenosis. The use of SAVAYSA is not recommended in these patients *[see Clinical Studies (14.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information.

- Increased risk of stroke with discontinuation of SAVAYSA in patients with NVAF *[see Warnings and Precautions (5.2)]*
- Spinal/epidural anesthesia or puncture *[see Warnings and Precautions (5.4)]*

The most serious adverse reactions reported with SAVAYSA were related to bleeding *[see Warnings and Precautions (5.3)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of SAVAYSA was evaluated in the ENGAGE AF-TIMI 48 and Hokusai VTE studies including 11,130 patients exposed to SAVAYSA 60 mg and 7002 patients exposed to SAVAYSA 30 mg once daily *[see Clinical Studies (14)]*.

The ENGAGE AF-TIMI 48 Study

In the ENGAGE AF-TIMI 48 study, the median study drug exposure for the SAVAYSA and warfarin treatment groups was 2.5 years.

Bleeding was the most common reason for treatment discontinuation. Bleeding led to treatment discontinuation in 3.9% and 4.1% of patients in the SAVAYSA 60 mg and warfarin treatment groups, respectively.

In the overall population, Major Bleeding was lower in the SAVAYSA group compared to the warfarin group [HR 0.80 (0.70, 0.91), p<0.001]. Table 6.1 shows Major Bleeding events (percentage of patients with at least one bleeding event, per year) for the indicated population (CrCL ≤ 95 mL/min).

Table 6.1: Adjudicated Bleeding Events for NVAF Patients with CrCL ≤ 95 mL/min*

Event[a]	SAVAYSA 60 mg[b] N = 5417 n (%/year)	Warfarin N = 5485 n (%/year)	SAVAYSA 60 mg vs. Warfarin HR (95% CI)
Major Bleeding[c]	357 (3.1)	431 (3.7)	0.84 (0.73, 0.97)
Intracranial Hemorrhage (ICH)[d]	53 (0.5)	122 (1.0)	0.44 (0.32, 0.61)
Hemorrhagic Stroke	33 (0.3)	69 (0.6)	0.49 (0.32, 0.74)
Other ICH	20 (0.2)	55 (0.5)	0.37 (0.22, 0.62)
Gastrointestinal[e]	205 (1.8)	150 (1.3)	1.40 (1.13, 1.73)
Fatal Bleeding[f]	21 (0.2)	42 (0.4)	0.51 (0.30, 0.86)
ICH	19 (0.2)	36 (0.3)	0.54 (0.31, 0.94)
Non-intracranial	2 (<0.1)	6 (<0.1)	----

Abbreviations: HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, n = number of patients with events, N = number of patients in Safety population,

* The on treatment period is during treatment or within 2 days of stopping study treatment. The difference in hemorrhagic stroke rate from Table 14.1 is because Table 14.1 includes events occurring during treatment or within 3 days of stopping study treatment and this table only includes patients with CrCL ≤ 95 mL/min.

[a] A subject can be included in multiple sub-categories if he/she had an event for those categories.

[b] Includes all patients with CrCL ≤ 95 mL/min randomized to receive 60 mg once daily, including those who were dose-reduced to 30 mg once daily because of prespecified baseline conditions.

[c] A Major Bleeding event (the study primary safety endpoint) was defined as clinically overt bleeding that met one of the following criteria: fatal bleeding; symptomatic bleeding in a critical site such as retroperitoneal, intracranial, intraocular, intraspinal, intra-articular, pericardial, or intramuscular with compartment syndrome; a clinically overt bleeding event that caused a fall in hemoglobin of at least 2.0 g/dL (or a fall in hematocrit of at least 6.0% in the absence of hemoglobin data), when adjusted for transfusions (1 unit of transfusion = 1.0 g/dL drop in hemoglobin).

[d] ICH includes primary hemorrhagic stroke, subarachnoid hemorrhage, epidural/subdural hemorrhage, and ischemic stroke with major hemorrhagic conversion.

[e] Gastrointestinal (GI) bleeds include bleeding from upper and lower GI tract. Lower GI tract bleeding includes rectal bleeds.

[f] Fatal bleed is a bleeding event during the on treatment period and adjudicated as leading directly to death within 7 days.

The most common site of a Major Bleeding event was the gastrointestinal (GI) tract. Table 6.2 shows the number of and the rate at which patients experienced GI bleeding in the SAVAYSA 60 mg and warfarin treatment groups.

Table 6.2 Gastrointestinal Bleeding Events for NVAF Patients with CrCL ≤ 95 mL/min*

	SAVAYSA N= 5417 n (%/year)	Warfarin N= 5485 n (%/year)
Major Gastrointestinal (GI) Bleeding[a]	205 (1.78)	150 (1.27)
- Upper GI	123 (1.06)	88 (0.74)
- Lower GI[b]	85 (0.73)	64 (0.54)
GUSTO[c] Severe GI bleeding	16 (0.14)	17 (0.14)
Fatal GI bleeding	1 (<0.1)	2 (<0.1)

* During or within 2 days of stopping study treatment

[a] GI bleeding was defined by location as upper or lower GI

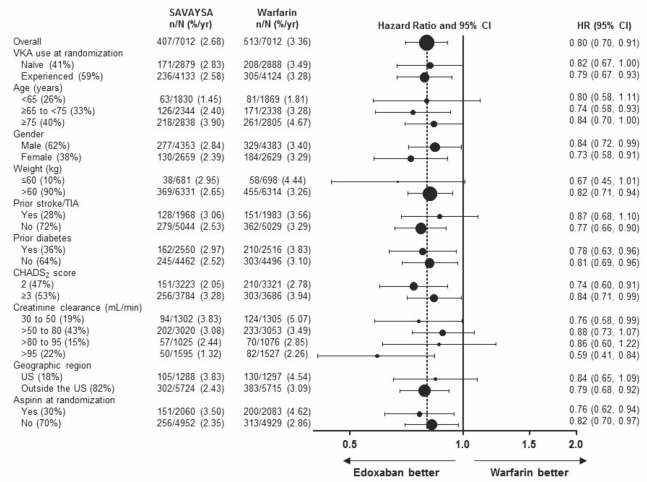
[b] Lower GI bleeding included anorectal bleeding

[c] GUSTO – Severe or life-threatening bleeding that caused hemodynamic compromise and requires intervention

The rate of anemia-related adverse events was greater with SAVAYSA 60 mg than with warfarin (9.6% vs. 6.8%).

The comparative rates of Major Bleeding on SAVAYSA and warfarin were generally consistent among subgroups (see Figure 6.1). Bleeding rates appeared higher in both treatment arms (SAVAYSA and warfarin) in the following subgroups of patients: those receiving aspirin, those in the United States, those more than 75 years old and those with reduced renal function.

Figure 6.1: Adjudicated Major Bleeding in the ENGAGE AF-TIMI 48* Study



*During or within 2 days of stopping study treatment

Note: The figure above presents effects in various subgroups all of which are baseline characteristics and most of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Other Adverse Reactions

The most common non-bleeding adverse reactions (≥ 1%) for SAVAYSA 60 mg versus warfarin were rash (4.2% vs. 4.1%), and abnormal liver function tests (4.8% vs. 4.6%), respectively.

Interstitial Lung Disease (ILD) was reported as a serious adverse event on treatment for SAVAYSA 60 mg and warfarin in 15 (0.2%) and 7 (0.1%) patients, respectively. Many of the cases in both treatment groups were confounded by the use of amiodarone, which has been associated with ILD, or by infectious pneumonia. In the overall study period, there were 5 and 0 fatal ILD cases in the SAVAYSA 60 mg and warfarin groups, respectively.

The Hokusai VTE Study

In the Hokusai VTE study, the duration of drug exposure for SAVAYSA was ≤ 6 months for 1561 (37.9%) of patients, > 6 months for 2557 (62.1%) of patients and 12 months for 1661 (40.3%) of patients.

Bleeding was the most common reason for treatment discontinuation and occurred in 1.4% and 1.4% of patients in the SAVAYSA and warfarin arms, respectively.

Bleeding in Patients with DVT and/or PE in the Hokusai VTE Study

The primary safety endpoint was Clinically Relevant Bleeding, defined as the composite of Major and Clinically Relevant Non-Major (CRNM) Bleeding that occurred during or within three days of stopping study treatment. The incidence of Clinically Relevant Bleeding was lower in SAVAYSA than warfarin [HR (95% CI): 0.81 (0.71, 0.94); p =0.004].

Table 6.3 shows the number of patients experiencing bleeding events in the Hokusai VTE Study.

Table 6.3: Bleeding Events in the Hokusai VTE Study

	SAVAYSA (N=4118)	Warfarin (N=4122)
Clinically Relevant Bleeding[a] (Major/CRNM), n (%)	349 (8.5)	423 (10.3)
Major Bleeding[b], n (%)	56 (1.4)	66 (1.6)
Fatal bleeding	2 (<0.1)	10 (0.2)
Intracranial fatal	0 (0.0)	6 (0.1)
Non-fatal critical organ bleeding	13 (0.3)	25 (0.6)
Intracranial bleeding	5 (0.1)	12 (0.3)
Non-fatal non-critical organ bleeding	41 (1.0)	33 (0.8)
Decrease in Hb ≥ 2g/dL	40 (1.0)	33 (0.8)
Transfusion of ≥ 2 units of RBC	28 (0.7)	22 (0.5)
CRNM Bleeding[c]	298 (7.2)	368 (8.9)
Any Bleed	895 (21.7)	1056 (25.6)

Abbreviations: N=number of patients in the modified intent-to-treat population; n = number of events; CRNM = clinically relevant non-major

[a] Primary Safety Endpoint: Clinically Relevant Bleeding (composite of Major and CRNM).

[b] A Major Bleeding event was defined as clinically overt bleeding that met one of the following criteria: associated with a fall in hemoglobin level of 2.0 g/dL or more, or leading to transfusion of two or more units of packed red cells or whole blood; occurring in a critical site or organ: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; contributing to death.

[c] CRNM bleeding was defined as overt bleeding not meeting the criteria for a Major Bleeding event but that was associated with a medical intervention, an unscheduled contact (visit or telephone call) with a physician, temporary cessation of study treatment, or associated with discomfort for the subject such as pain, or impairment of activities of daily life.

Patients with low body weight (≤ 60 kg), CrCL ≤ 50 mL/min, or concomitant use of select P-gp inhibitors were randomized to receive SAVAYSA 30 mg or warfarin. As compared to all patients who received SAVAYSA or warfarin in the 60 mg cohort, all patients who received SAVAYSA or warfarin in the 30 mg cohort (n= 1452, 17.6% of the entire study population) were older (60.1 vs 54.9 years), more frequently female (66.5% vs 37.7%), more frequently of Asian race (46.0% vs 15.6%) and had more co-morbidities (e.g., history of bleeding, hypertension, diabetes, cardiovascular disease, cancer). Clinically relevant bleeding events occurred in 58/733 (7.9%) of the SAVAYSA patients receiving 30 mg once daily and 92/719 (12.8%) of warfarin patients meeting the above criteria.

In the Hokusai VTE study, among all patients the most common bleeding adverse reactions (≥ 1%) are shown in Table 6.4.

Table 6.4: Adverse Reactions Occurring in ≥ 1% of Patients Treated in Hokusai VTE

	SAVAYSA 60 mg (N=4118) n (%)	Warfarin (N=4122) n (%)
Bleeding ADRs[a]		
Vaginal[b]	158 (9.0)	126 (7.1)
Cutaneous soft tissue	245 (5.9)	414 (10.0)
Epistaxis	195 (4.7)	237 (5.7)
Gastrointestinal bleeding	171 (4.2)	150 (3.6)
Lower gastrointestinal	141 (3.4)	126 (3.1)
Oral/pharyngeal	138 (3.4)	162 (3.9)
Macroscopic hematuria/urethral	91 (2.2)	117 (2.8)
Puncture site	56 (1.4)	99 (2.4)
Non-Bleeding ADRs		
Rash	147 (3.6)	151 (3.7)
Abnormal liver function tests	322 (7.8)	322 (7.8)
Anemia	72 (1.7)	55 (1.3)

[a] Adjudicated Any Bleeding by location for all bleeding event categories (including Major and CRNM)

[b] Gender specific vaginal bleeding percentage is based on number of female subjects in each treatment group

7 DRUG INTERACTIONS

7.1 Anticoagulants, Antiplatelets, and Thrombolytics

Co-administration of anticoagulants, antiplatelet drugs, and thrombolytics may increase the risk of bleeding. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with anticoagulants, aspirin, other platelet aggregation inhibitors, and/or NSAIDs *[see Warnings and Precautions (5.3)]*.

Long-term concomitant treatment with SAVAYSA and other anticoagulants is not recommended because of increased risk of bleeding *[see Warnings and Precautions (5.3)]*. Short term co-administration may be needed for patients transitioning to or from SAVAYSA *[see Dosage and Administration (2.4)]*.

In clinical studies with SAVAYSA concomitant use of aspirin (low dose ≤ 100 mg/day) or thienopyridines, and NSAIDs was permitted and resulted in increased rates of Clinically Relevant Bleeding. Carefully monitor for bleeding in patients who require chronic treatment with low dose aspirin and/or NSAIDs *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

7.2 P-gp Inducers

Avoid the concomitant use of SAVAYSA with rifampin *[see Clinical Pharmacology (12.3)]*.

7.3 P-gp Inhibitors

Treatment of NVAF

Based on clinical experience from the ENGAGE AF-TIMI 48 study, dose reduction in patients concomitantly receiving P-gp inhibitors resulted in edoxaban blood levels that were lower than in patients who were given the full dose. Consequently, no dose reduction is recommended for concomitant P-gp inhibitor use *[see Dosage and Administration (2.1)*, *Clinical Pharmacology (12.3) and Clinical Studies (14.1)]*.

Treatment of Deep Vein Thrombosis and Pulmonary Embolism [see Clinical Studies (14.2)]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies in pregnant women. SAVAYSA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data

In the Hokusai VTE study there were 10 pregnancy cases reported in patients receiving SAVAYSA with exposure in the first trimester and estimated duration of exposure for up to approximately 6 weeks. Among these there were 6 live births (4 full term, 2 pre-term), 1 first-trimester spontaneous abortion, and 3 cases of elective termination of pregnancy.

Animal Data

Embryo-fetal development studies were conducted in pregnant rats and rabbits during the period of organogenesis. In rats, no teratogenic effects were seen when edoxaban was administered orally at doses up to 300 mg/kg/day, or 49 times the human dose of 60 mg/day normalized to body surface area. Increased post-implantation loss occurred at 300 mg/kg/day, but this effect may be secondary to the maternal vaginal hemorrhage seen at this dose. In rabbits, no teratogenic effects were seen at doses up to 600 mg/kg/day (49 times the human exposure at a dose of 60 mg/day when based on AUC). Embryo-fetal toxicities occurred at maternally toxic doses, and included absent or small fetal gallbladder at 600 mg/kg/day, and increased post-implantation loss, increased spontaneous abortion, and decreased live fetuses and fetal weight at doses equal to or greater than 200 mg/kg/day, which is equal to or greater than 20 times the human exposure.

In a rat pre- and post-natal developmental study, edoxaban was administered orally during the period of organogenesis and through lactation day 20 at doses up to 30 mg/kg/day, which is up to 3 times the human exposure when based on AUC. Vaginal bleeding in pregnant rats and delayed avoidance response (a learning test) in female offspring were seen at 30 mg/kg/day.

8.2 Labor and Delivery

Safety and effectiveness of SAVAYSA during labor and delivery have not been studied in clinical studies. The risks of bleeding should be balanced with the risk of thrombotic events when considering the use of SAVAYSA in this setting.

8.3 Nursing Mothers

It is not known if edoxaban is excreted in human milk. Edoxaban was excreted in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from SAVAYSA, a decision should be made to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total patients in the ENGAGE AF-TIMI 48 study, 5182 (74%) were 65 years and older, while 2838 (41%) were 75 years and older. In Hokusai VTE, 1334 (32%) patients were 65 years and older, while 560 (14%) patients were 75 years and older. In clinical trials the efficacy and safety of SAVAYSA in elderly (65 years or older) and younger patients were similar *[see Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)*, *and Clinical Studies (14)]*.

8.6 Renal Impairment

Renal clearance accounts for approximately 50% of the total clearance of edoxaban. Consequently, edoxaban blood levels are increased in patients with poor renal function compared to those with higher renal function. Reduce SAVAYSA dose to 30 mg once daily in patients with CrCL 15-50 mL/min. There are limited clinical data with SAVAYSA in patients with CrCL < 15 mL/min; SAVAYSA is therefore not recommended in these patients. Hemodialysis does not significantly contribute to SAVAYSA clearance *[see Dosage and Administration (2.1, 2.2) and Clinical Pharmacology (12.3)]*.

As renal function improves and edoxaban blood levels decrease, the risk for ischemic stroke increases in patients with NVAF *[see Indications and Usage (1.1)*, *Dosage and Administration (2.1)*, *and Clinical Studies (14.1)]*.

8.7 Hepatic Impairment

The use of SAVAYSA in patients with moderate or severe hepatic impairment (Child-Pugh B and C) is not recommended as these patients may have intrinsic coagulation abnormalities. No dose reduction is required in patients with mild hepatic impairment (Child-Pugh A) *[see Clinical Pharmacology (12.3)]*.

8.8 Low Body Weight Consideration for Patients treated for DVT and/or PE

Based on the clinical experience from the Hokusai VTE study, reduce SAVAYSA dose to 30 mg in patients with body weight less than or equal to 60 kg *[see Dosage and Administration (2.2) and Clinical Studies (14.2)]*.

10 OVERDOSAGE

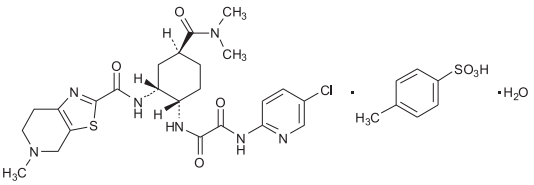
A specific reversal agent for edoxaban is not available. Overdose of SAVAYSA increases the risk of bleeding.

The following are not expected to reverse the anticoagulant effects of edoxaban: protamine sulfate, vitamin K, and tranexamic acid *[see Warnings and Precautions (5.3)]*.

Hemodialysis does not significantly contribute to edoxaban clearance *[see Pharmacokinetics (12.3)]*.

11 DESCRIPTION

Edoxaban, a factor Xa inhibitor, is supplied as edoxaban tosylate monohydrate. The chemical name is *N*-(5-Chloropyridin-2-yl)-*N'*-[(1*S*,2*R*,4*S*)-4-(*N*,*N*-dimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydro[1,3]thiazolo[5,4-*c*]pyridine-2-carboxamido)cyclohexyl] oxamide mono (4-methylbenzenesulfonate) monohydrate. Edoxaban tosylate monohydrate has the empirical formula $C_{24}H_{30}ClN_7O_4S \bullet C_7H_8O_3S \bullet H_2O$ representing a molecular weight of 738.27. The chemical structure of edoxaban tosylate monohydrate is:



It is a white to pale yellowish-white crystalline powder. The solubility of edoxaban tosylate (pKa 6.7) decreases with increasing pH. It is slightly soluble in water, pH 3 to 5 buffer, very slightly soluble at pH 6 to 7; and practically insoluble at pH 8 to 9.

SAVAYSA is available for oral administration as a 60 mg, 30 mg, or 15 mg round shaped, film-coated tablet, debossed with product identification markings. Each 60 mg tablet contains 80.82 mg edoxaban tosylate monohydrate equivalent to 60 mg of edoxaban. Each 30 mg tablet contains 40.41 mg edoxaban tosylate monohydrate equivalent to 30 mg of edoxaban. Each 15 mg tablet contains 20.20 mg edoxaban tosylate monohydrate equivalent to 15 mg of edoxaban. The inactive ingredients are: mannitol, pregelatinized starch, crospovidone, hydroxypropyl cellulose, magnesium stearate, talc, and carnauba wax. The color coatings contain hypromellose, titanium dioxide, talc, polyethylene glycol 8000, iron oxide yellow (60 mg tablets and 15 mg tablets), and iron oxide red (30 mg tablets and 15 mg tablets).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Edoxaban is a selective inhibitor of FXa. It does not require antithrombin III for antithrombotic activity. Edoxaban inhibits free FXa, and prothrombinase activity and inhibits thrombin-induced platelet aggregation. Inhibition of FXa in the coagulation cascade reduces thrombin generation and reduces thrombus formation.

12.2 Pharmacodynamics

As a result of FXa inhibition, edoxaban prolongs clotting time tests such as prothrombin time (PT), and activated partial thromboplastin time (aPTT). Changes observed in PT, INR, and aPTT at the expected therapeutic dose, however, are small, subject to a high degree of variability and not useful in

monitoring the anticoagulant effect of edoxaban. Following oral administration, peak pharmacodynamic effects are observed within 1-2 hours, which correspond with peak edoxaban concentrations (C_{max}).

Cardiac Electrophysiology
In a thorough QT study in healthy men and women aged 19-45 years, no QTc interval prolongation was observed with edoxaban (90 mg and 180 mg).

Effect of PCCs on Pharmacodynamics of SAVAYSA
There is no systematic evaluation of bleeding reversal by 4-factor prothrombin complex concentrate (PCC) products in patients who have received SAVAYSA.

Effects of PCC (50 IU/kg) on the pharmacodynamics of edoxaban were studied in healthy subjects following a punch biopsy. Following administration of a single dose of edoxaban, endogenous thrombin potential (ETP) returned to pre-edoxaban baseline levels in 0.5 hours after the initiation of a 15 minute infusion of 50 IU/kg PCC, compared to more than 24 hours with placebo. Mean ETP levels continued to increase and exceeded pre-edoxaban baseline, reaching maximum elevations (~40% over pre-edoxaban levels) at 22 hours after initiating PCC dose, which was the last observation of ETP. The clinical relevance of this ETP increase is unknown.

Pharmacodynamic Interactions
Aspirin
Co-administration of aspirin (100 mg or 325 mg) and edoxaban increased bleeding time relative to that seen with either drug alone.

NSAID (Naproxen)
Co-administration of naproxen (500 mg) and edoxaban increased bleeding time relative to that seen with either drug alone.

12.3 Pharmacokinetics
Edoxaban displays approximately dose-proportional pharmacokinetics for doses of 15 to 150 mg and 60 to 120 mg following single and repeat doses, respectively, in healthy subjects.

Absorption
Following oral administration, peak plasma edoxaban concentrations are observed within 1-2 hours. Absolute bioavailability is 62%. Food does not affect total systemic exposure to edoxaban. SAVAYSA was administered with or without food in the ENGAGE AF-TIMI 48 and Hokusai VTE trials. No data are available regarding the bioavailability upon crushing and/or mixing of edoxaban tablets into food, liquids, or administration through feeding tubes.

Distribution
Disposition is biphasic. The steady-state volume of distribution (Vd_{ss}) is 107 (19.9) L [mean (SD)]. *In vitro* plasma protein binding is approximately 55%. There is no clinically relevant accumulation of edoxaban (accumulation ratio 1.14) with once daily dosing.

Steady-state concentrations are achieved within 3 days.

Metabolism
Unchanged edoxaban is the predominant form in plasma. There is minimal metabolism via hydrolysis (mediated by carboxylesterase 1), conjugation, and oxidation by CYP3A4.

The predominant metabolite M-4, formed by hydrolysis, is human-specific and active and reaches less than 10% of the exposure of the parent compound in healthy subjects. Exposure to the other metabolites is less than 5% of exposure to edoxaban.

Elimination
Edoxaban is eliminated primarily as unchanged drug in the urine. Renal clearance (11 L/hour) accounts for approximately 50% of the total clearance of edoxaban (22 L/hour). Metabolism and biliary/intestinal excretion account for the remaining clearance. The terminal elimination half-life of edoxaban following oral administration is 10 to 14 hours.

Specific Populations
Hepatic Impairment
In a dedicated pharmacokinetic study, patients with mild or moderate hepatic impairment (classified as Child-Pugh A or Child-Pugh B) exhibited similar pharmacokinetics and pharmacodynamics to their matched healthy control group. There is no clinical experience with edoxaban in patients with severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

Renal Impairment
In a dedicated pharmacokinetic study, total systemic exposure to edoxaban for subjects with CrCL > 50 to < 80 mL/min, CrCL 30 to 50 mL/min, CrCL < 30 mL/min, or undergoing peritoneal dialysis, were increased by 32%, 74%, 72%, and 93%, respectively, relative to subjects with CrCL ≥ 80 mL/min *[see Use in Specific Populations (8.6)]*.

Hemodialysis
A 4-hour hemodialysis session reduced total edoxaban exposure by less than 7%.

Age
In a population pharmacokinetic analysis, after taking renal function and body weight into account, age had no additional clinically significant effect on edoxaban pharmacokinetics.

Weight
In a population pharmacokinetic analysis, total exposure in patients with median low body weight (55 kg) was increased by 13% as compared with patients with median high body weight (84 kg).

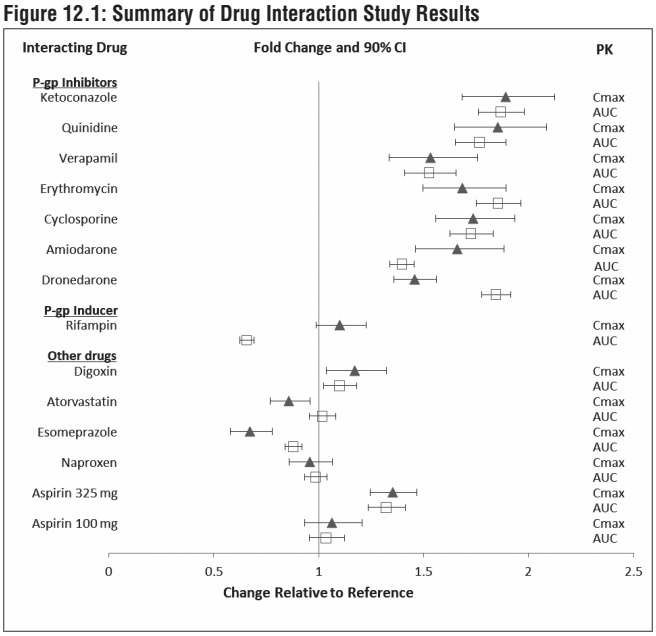
Gender
In a population pharmacokinetic analysis, after accounting for body weight, gender had no additional clinically significant effect on edoxaban pharmacokinetics.

Race
In a population pharmacokinetic analysis, edoxaban exposures in Asian patients and non-Asian patients were similar.

Drug Interactions
In vitro Drug Interactions Studies
In vitro studies indicate that edoxaban does not inhibit the major cytochrome P450 enzymes (CYP1A2, 2A6, 2B6, 2C8/9, 2C19, 2D6, 2E1, or 3A4) and does not induce CYP1A2, CYP3A4 or the P-gp transporter (MDR1). *In vitro* data also indicate that edoxaban does not inhibit the following transporters at clinically relevant concentrations: P-gp, the organic anion transporters OAT1 or OAT3; the organic cation transporters OCT1 or OCT2; or the organic ion transporting polypeptides OATP1B1 or OATP1B3. Edoxaban is a substrate of P-gp transporter.

Impact of Other Drugs on SAVAYSA
The effect of co-administered amiodarone, cyclosporine, dronedarone, erythromycin, ketoconazole, quinidine, verapamil, and rifampin on edoxaban exposure is shown in Figure 12.1.

Figure 12.1: Summary of Drug Interaction Study Results



Impact of Edoxaban on Other Drugs
Edoxaban increased the C_{max} of concomitantly administered digoxin by 28%; however, the AUC was not affected. Edoxaban had no effect on the C_{max} and AUC of quinidine.

Edoxaban decreased the C_{max} and AUC of concomitantly administered verapamil by 14% and 16%, respectively.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Edoxaban was not carcinogenic when administered daily to mice and rats by oral gavage for up to 104 weeks. The highest dose tested (500 mg/kg/day) in male and female mice was 3 and 6 times, respectively, the human exposure (AUC) at the human dose of 60 mg/day, and the highest doses tested in male (600/400 mg/kg/day) and female (200 mg/kg/day) rats were 8 and 14 times, respectively, the human exposure at the human dose of 60 mg/day.

Edoxaban and its human-specific metabolite, M-4, were genotoxic in *in vitro* chromosomal aberration tests but were not genotoxic in the *in vitro* bacterial reverse mutation (Ames test), in *in vitro* human lymphocytes micronucleus test, in *in vivo* rat bone marrow micronucleus test, in *in vivo* rat liver micronucleus test, and in *in vivo* unscheduled DNA synthesis tests.

Edoxaban showed no effects on fertility and early embryonic development in rats at doses of up to 1000 mg/kg/day (162 times the human dose of 60 mg/day normalized to body surface area).

14 CLINICAL STUDIES

14.1 Nonvalvular Atrial Fibrillation

The ENGAGE AF-TIMI 48 Study

The ENGAGE AF-TIMI 48 study was a multi-national, double-blind, non-inferiority study comparing the efficacy and safety of two SAVAYSA treatment arms (60 mg and 30 mg) to warfarin (titrated to INR 2.0 to 3.0) in reducing the risk of stroke and systemic embolic events in patients with NVAF. The non-inferiority margin (degree of inferiority of SAVAYSA to warfarin that was to be ruled out) was set at 38%, reflecting the substantial effect of warfarin in reducing strokes. The primary analysis included both ischemic and hemorrhagic strokes.

To enter the study, patients had to have one or more of the following additional risk factors for stroke:

- a prior stroke (ischemic or unknown type), transient ischemic attack (TIA) or non-CNS systemic embolism, or
- 2 or more of the following risk factors:
  - age ≥ 75 years,
  - hypertension,
  - heart failure, or
  - diabetes mellitus

A total of 21,105 patients were randomized and followed for a median of 2.8 years and treated for a median of 2.5 years. Patients in the SAVAYSA treatment arms had their dose halved (60 mg halved to 30 mg or 30 mg halved to 15 mg) if one or more of the following clinical factors were present: CrCL ≤ 50 mL/min, low body weight (≤ 60 kg) or concomitant use of specific P-gp inhibitors (verapamil, quinidine, dronedarone). Patients on antiretroviral therapy (ritonavir, nelfinavir, indinavir, saquinavir) as well as cyclosporine were excluded from the study. Approximately 25% of patients in all treatment groups received a reduced dose at baseline, and an additional 7% were dose-reduced during the study. The most common reason for dose reduction was a CrCL ≤ 50 mL/min at randomization (19% of patients).

Patients were well balanced with respect to demographic and baseline characteristics. The percentages of patients age ≥ 75 years and ≥ 80 years were approximately 40% and 17%, respectively. The majority of patients were Caucasian (81%) and male (62%). Approximately 40% of patients had not taken a Vitamin K Antagonist (VKA) (i.e., never took a VKA or had not taken a VKA for more than 2 months).

The mean patient body weight was 84 kg (185 lbs) and 10% of patients had a body weight of ≤ 60 kg. Concomitant diseases of patients in this study included hypertension (94%), congestive heart failure (58%), and prior stroke or transient ischemic attack (28%). At baseline, approximately 30% of patients were on aspirin and approximately 2% of patients were taking a thienopyridine.

Patients randomized to the warfarin arm achieved a mean TTR (time in therapeutic range, INR 2.0 to 3.0) of 65% during the course of the study.

The primary endpoint of the study was the occurrence of first stroke (either ischemic or hemorrhagic) or of a systemic embolic event (SEE) that occurred during treatment or within 3 days from the last dose taken. In the overall results of the study, shown in Table 14.1, both treatment arms of SAVAYSA were non-inferior to warfarin for the primary efficacy endpoint of stroke or SEE. However, the 30 mg (15 mg dose-reduced) treatment arm was numerically less effective than warfarin for the primary endpoint, and was also markedly inferior in reducing the rate of ischemic stroke. Based on the planned superiority analysis (ITT, which required $p < 0.01$ for success), statistical superiority of the 60 mg (30 mg dose-reduced) treatment arm compared to warfarin was not established in the total study population, but there was a favorable trend [HR (99% CI): 0.87 (0.71, 1.07)].

Table 14.1: Strokes and Systemic Embolic Events in the ENGAGE AF-TIMI 48 Study (mITT, on Treatment[a])

Events	SAVAYSA 30 mg[b] (N=7002) n (%/yr)[c]	SAVAYSA 60 mg[b] (N=7012) n (%/yr)[c]	Warfarin (N=7012) n (%/yr)[c]	SAVAYSA 30 mg vs. warfarin HR (CI)[d] p-value	SAVAYSA 60 mg vs. warfarin HR (CI)[d] p-value
First Stroke or SEE	253 (1.6)	182 (1.2)	232 (1.5)	1.07 (0.87, 1.31) p=0.44	0.79 (0.63, 0.99) p=0.017
Ischemic Stroke	225 (1.4)	135 (0.9)	144 (0.9)	1.54 (1.25, 1.90)	0.94 (0.75, 1.19)
Hemorrhagic Stroke	18 (0.1)	39 (0.3)	75 (0.5)	0.24 (0.14, 0.39)	0.52 (0.36, 0.77)
Systemic Embolism	10 (<0.1)	8 (<0.1)	13 (<0.1)	0.75 (0.33, 1.72)	0.62 (0.26, 1.50)

Abbreviations: HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, n = number of events, mITT = Modified Intent-to-Treat, N=number of patients in mITT population, SEE = Systemic Embolic Event, yr = year.

[a] Includes events during treatment or within 3 days of stopping study treatment

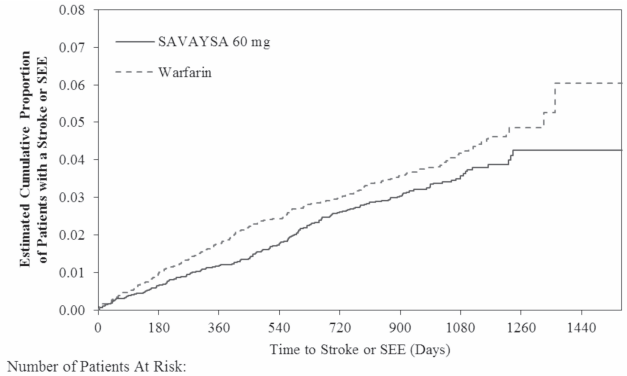
[b] Includes patients dose-reduced to 15 mg for the 30 mg treatment group and 30 mg for the 60 mg treatment group

[c] The event rate (%/yr) is calculated as number of events/subject-year exposure.

[d] 97.5% CI for primary endpoint of First Stroke or SEE. 95% CI for Ischemic Stroke, Hemorrhagic Stroke or Systemic Embolism

Figure 14.1 is a plot of the time from randomization to the occurrence of the first primary endpoint in all patients randomized to 60 mg SAVAYSA or warfarin.

Figure 14.1: Kaplan-Meier Cumulative Event Rate Estimates for Primary Endpoint (first occurrence of stroke or SEE) (mITT*)



Number of Patients At Risk:

SAVAYSA	7012	5699	5056	2213	46
Warfarin	7012	5724	5108	2186	55

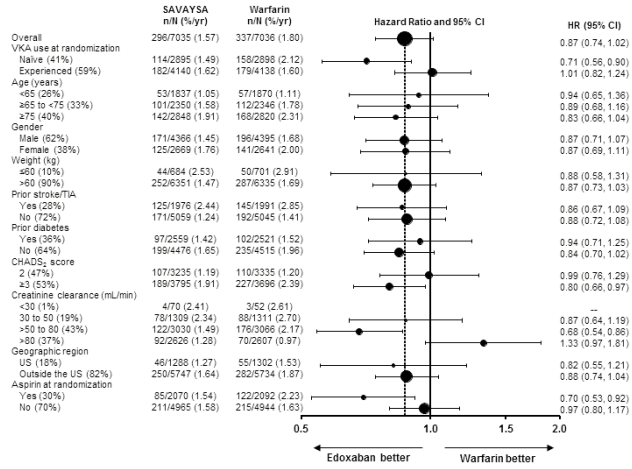
* On treatment Study Period defined as Initial Dose to Final Dose + three days

The incidence rate of the primary endpoint of stroke or SEE in patients (N=1776) treated with the 30 mg reduced dose of SAVAYSA because of a CrCL level ≤ 50 mL/min, low body weight ≤ 60 kg, or the concomitant use of a P-gp inhibitor drug, was 1.79% per year. Patients with any of these characteristics who were randomized to receive warfarin had an incidence rate of the primary endpoint of 2.21% per year [HR (95% CI): 0.81 (0.58, 1.13)].

In all randomized patients during the overall study period, the rates of CV death with SAVAYSA and warfarin were 2.74% per year vs. 3.17% per year, respectively [HR (95% CI): 0.86 (0.77, 0.97)].

The results in the ENGAGE AF-TIMI 48 study for the primary efficacy endpoint for most major subgroups are displayed in Figure 14.2.

Figure 14.2: ENGAGE AF-TIMI 48 Study: Primary Efficacy Endpoint by Subgroups (ITT Analysis Set)



Note: The figure above presents effects in various subgroups all of which are baseline characteristics and most of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

The results of the ENGAGE AF-TIMI 48 study show a strong relationship between the blood levels of edoxaban and its effectiveness in reducing the rate of ischemic stroke. There was a 64% increase in the ischemic stroke rate in patients in the 30 mg treatment arm (including patients with dose reduced to 15 mg) compared to the 60 mg treatment arm (including patients with dose reduced to 30 mg). Approximately half of the SAVAYSA dose is eliminated by the kidney, and edoxaban blood levels are lower in patients with better renal function, averaging about 30% less in patients with CrCL of > 80 mL/min, and 40% less in patients with CrCL > 95 mL/min when compared to patients with a CrCL of > 50 to ≤ 80 mL/min. Given the clear relationship of dose and blood levels to effectiveness in the ENGAGE AF-TIMI 48 study, it could be anticipated that patients with better renal function would show a smaller effect of SAVAYSA compared to warfarin than would patients with mildly impaired renal function, and this was in fact observed.

Table 14.2 shows the results for the study primary efficacy endpoint of first stroke or SEE as well as the effects on ischemic and hemorrhagic stroke in the pre-randomization CrCL subgroups for SAVAYSA 60 mg (including 30 mg dose-reduced) and warfarin. There was a decreased rate of ischemic stroke with SAVAYSA 60 mg compared to warfarin in patients with CrCL > 50 to ≤ 80 mL/min [HR (95% CI): 0.63 (0.44, 0.89)]. In patients with CrCL > 80 to ≤ 95 mL/min the results for ischemic stroke slightly favor warfarin with a confidence interval that crosses 1.0 [HR (95% CI): 1.11 (0.58, 2.12)]. The rate of ischemic stroke was higher relative to warfarin in the patients with CrCL > 95 mL/min [HR (95% CI): 2.16 (1.17, 3.97)]. Pharmacokinetic data indicate that patients with CrCL > 95 mL/min had lower plasma edoxaban levels, along with a lower rate of bleeding relative to warfarin than patients with CrCL ≤ 95 mL/min. Consequently, SAVAYSA should not be used in patients with CrCL > 95 mL/min *[see Dosage and Administration (2.1), Warnings and Precautions (5.1), Adverse Reactions (6.1), and Clinical Pharmacology (12.3)]*.

In patients with CrCL ≤ 95 mL/min, the SAVAYSA 60 mg (30 mg dose-reduced) treatment arm reduced the risk of stroke or SEE when compared to warfarin [HR (95% CI): 0.68 (0.55, 0.84)].

In the indicated population (CrCL ≤ 95 mL/min), during the overall study period, the rates of CV death with SAVAYSA and warfarin were 2.95% per year vs. 3.59% per year, respectively [HR (95% CI): 0.82 (0.72, 0.93)].

Table 14.2: Primary Endpoint, Ischemic and Hemorrhagic Stroke Results in as a Function of Baseline Creatinine Clearance (mITT Population, On Treatment)

STROKE TYPE Renal Function Subgroups[a]	Treatment Arm	n (N)	Event Rate (%/yr)	SAVAYSA 60 mg vs. Warfarin HR (95% CI)
PRIMARY ENDPOINT (STROKE/SEE)				
≤ 95 (Indicated Population)	Warfarin	211 (5485)	1.8	
	SAVAYSA 60 mg	142 (5417)	1.2	0.68 (0.55, 0.84)
≤ 50[b]	Warfarin	50 (1356)	2.0	
	SAVAYSA 60 mg	45 (1372)	1.8	0.90 (0.60, 1.34)
> 50 to ≤ 80	Warfarin	135 (3053)	2.0	
	SAVAYSA 60 mg	71 (3020)	1.1	0.53 (0.40, 0.70)
> 80 to ≤ 95	Warfarin	26 (1076)	1.0	
	SAVAYSA 60 mg	26 (1025)	1.1	1.05 (0.61, 1.82)
> 95*	Warfarin	21 (1527)	0.6	
	SAVAYSA 60 mg	40 (1595)	1.0	1.87 (1.10, 3.17)
ISCHEMIC STROKE				
≤ 95 (Indicated Population)	Warfarin	129 (5485)	1.1	
	SAVAYSA 60 mg	102 (5417)	0.9	0.80 (0.62, 1.04)
≤ 50[b]	Warfarin	28 (1356)	1.1	
	SAVAYSA 60 mg	31 (1372)	1.2	1.11 (0.66, 1.84)
> 50 to ≤ 80	Warfarin	83 (3053)	1.2	
	SAVAYSA 60 mg	52 (3020)	0.8	0.63 (0.44, 0.89)
> 80 to ≤ 95	Warfarin	18 (1076)	0.7	
	SAVAYSA 60 mg	19 (1025)	0.8	1.11 (0.58, 2.12)
> 95*	Warfarin	15 (1527)	0.4	
	SAVAYSA 60 mg	33 (1595)	0.9	2.16 (1.17, 3.97)
HEMORRHAGIC STROKE				
≤ 95 (Indicated Population)	Warfarin	70 (5485)	0.6	
	SAVAYSA 60 mg	34 (5417)	0.3	0.50 (0.33, 0.75)
≤ 50[b]	Warfarin	18 (1356)	0.7	
	SAVAYSA 60 mg	12 (1372)	0.5	0.66 (0.32, 1.36)
> 50 to ≤ 80	Warfarin	45 (3053)	0.7	
	SAVAYSA 60 mg	17 (3020)	0.3	0.38 (0.22, 0.67)

(continued)

Table 14.2: Primary Endpoint, Ischemic and Hemorrhagic Stroke Results in as a Function of Baseline Creatinine Clearance (mITT Population, On Treatment)

STROKE TYPE Renal Function Subgroups[a]	Treatment Arm	n (N)	Event Rate (%/yr)	SAVAYSA 60 mg vs. Warfarin HR (95% CI)
HEMORRHAGIC STROKE				
> 80 to ≤ 95	Warfarin	7 (1076)	0.3	
	SAVAYSA 60 mg	5 (1025)	0.2	0.76 (0.24, 2.38)
> 95*	Warfarin	6 (1527)	0.2	
	SAVAYSA 60 mg	6 (1595)	0.2	0.98 (0.31, 3.05)

Abbreviations: HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, n = number of events, mITT = Modified Intent-to-Treat, N=number of patients in mITT population, yr = year.

* See Boxed Warning

[a] Renal function subgroups are based on estimated creatinine clearance in mL/min calculated using the Cockcroft-Gault formula.

[b] 83% of patients with pre-randomization CrCL ≤ 50 mL/min in the SAVAYSA 60 mg group were dose-reduced and consequently received SAVAYSA 30 mg daily. All patients in the warfarin group with CrCL ≤ 50 mL/min were treated in the same way as those with higher levels of CrCL.

Transition to Other Anticoagulants in the ENGAGE AF-TIMI 48 Study

In the ENGAGE AF-TIMI 48 study, the schemes for transitioning from study medication to open-label warfarin at the end of study were associated with similar rates of stroke and systemic embolism in the SAVAYSA 60 mg and warfarin groups *[see Dosage and Administration (2.4)]*. In the SAVAYSA 60 mg group 7 (0.2%) of 4529 patients had a stroke or SEE compared to 7 (0.2%) of 4506 patients in the warfarin arm.

14.2 Treatment of Deep Vein Thrombosis and Pulmonary Embolism

The Hokusai VTE Study

SAVAYSA for the treatment of patients with deep vein thrombosis (DVT) and pulmonary embolism (PE) was studied in a multi-national, double-blind study (Hokusai VTE) which compared the efficacy and safety of SAVAYSA 60 mg orally once daily to warfarin (titrated to INR 2.0 to 3.0) in patients with acute symptomatic venous thromboembolism (VTE) (DVT or PE with or without DVT). All patients had VTE confirmed by appropriate diagnostic imaging at baseline and received initial heparin therapy with low molecular weight heparin (LMWH) or unfractionated heparin for at least 5 days [median LMWH/heparin treatment in the SAVAYSA 60 mg group was 7 days, and in the warfarin group it was 8.0 days] and until INR (sham or real) was ≥ 2.0 on two measurements. Blinded drug treatment in the warfarin arm was started concurrently with initial heparin therapy and in the SAVAYSA arm after discontinuation of initial heparin. Patients randomized to SAVAYSA received 30 mg once daily if they met one or more of the following criteria: CrCL 30 to 50 mL/min, body weight ≤ 60 kg, or concomitant use of specific P-gp inhibitors (verapamil and quinidine or the short-term concomitant administration of azithromycin, clarithromycin, erythromycin, oral itraconazole or oral ketoconazole). The edoxaban dosage regimen was to be returned to the regular dosage of 60 mg once daily at any time the subject is not taking the concomitant medication provided no other criteria for dose reduction are met. Other P-gp inhibitors were not permitted in the study. Patients on antiretroviral therapy (ritonavir, nelfinavir, indinavir, saquinavir) as well as cyclosporine were excluded from the Hokusai VTE study. The concomitant use of these drugs with SAVAYSA has not been studied in patients. The treatment duration was from 3 months up to 12 months, determined by investigator based on patient clinical features. Patients were excluded if they required thrombectomy, insertion of a caval filter, use of a fibrinolytic agent, or use of other P-gp inhibitors, had a creatinine clearance < 30 mL/min, significant liver disease, or active bleeding. The primary efficacy outcome was symptomatic VTE, defined as the composite of recurrent DVT, new non-fatal symptomatic PE, and fatal PE during the 12-month study period.

A total of 8292 patients were randomized to receive SAVAYSA or warfarin and were followed for a mean treatment duration of 252 days for SAVAYSA and 250 days for warfarin. The mean age was approximately 56 years. The population was 57% male, 70% Caucasian, 21% Asian, and about 4% Black. The presenting diagnosis was PE (with or without DVT) in 40.7% and DVT only in 59.3% of patients. At baseline, 27.6% of patients had temporary risk factors only (e.g., trauma, surgery, immobilization, estrogen therapy). Overall 9.4% had a history of cancer, 17.3% of the patients had an age ≥ 75 years and/or a body weight ≤ 50 kg, and/or a CrCL < 50 mL/min, and 31.4% of patients had NT-ProBNP ≥ 500 pg/mL.

Aspirin was taken as on treatment concomitant antithrombotic medication by approximately 9% of patients in both groups.

In the warfarin group, the median TTR (time in therapeutic range, INR 2.0 to 3.0) was 65.6%.

A total of 8240 patients (n= 4118 for SAVAYSA and n = 4122 for warfarin) received study drug and were included in the modified intent-to-treat (mITT) population. SAVAYSA was demonstrated to be non inferior to warfarin for the primary endpoint of recurrent VTE [HR (95% CI): 0.89 (0.70, 1.13)] (Table 14.3, Figure 14.3).

Table 14.3: Primary Composite Efficacy Endpoint Results in Hokusai VTE (mITT Overall Study Period)

Primary Endpoint	SAVAYSA [a] n/N (%)	Warfarin n/N (%)	SAVAYSA vs. Warfarin HR (95% CI)
All patients with symptomatic recurrent VTE[b]	130/4118 (3.2)	146/4122 (3.5)	0.89 (0.70,1.13)
PE with or without DVT	73/4118 (1.8)	83/4122 (2.0)	-
Fatal PE and Death where PE cannot be ruled out	24/4118 (0.6)	24/4122 (0.6)	-
Non-fatal PE	49/4118 (1.2)	59/4122 (1.4)	-
DVT only	57/4118 (1.4)	63/4122 (1.5)	-
Index PE[c] patients with symptomatic recurrent VTE	47/1650 (2.8)	65/1669 (3.9)	-
Index DVT[d] patients with symptomatic recurrent VTE	83/2468 (3.4)	81/2453 (3.3)	-

Abbreviations: mITT = modified intent-to-treat; HR =hazard ratio vs. warfarin; CI =confidence interval; N=number of patients in mITT population; n = number of events

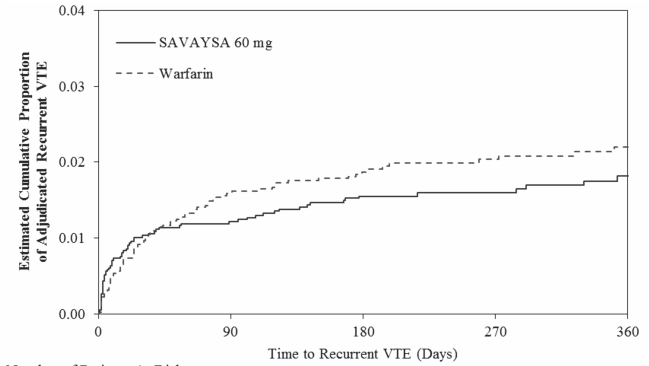
[a] Includes patients dose-reduced to 30 mg. Among the 1452 (17.6%) patients with low body weight (≤ 60 kg), moderate renal impairment (CrCL ≤ 50 mL/min), or concomitant use of P-gp inhibitors in the Hokusai VTE study, 22 (3.0%) of the SAVAYSA patients (30 mg once daily, n =733) and 30 (4.2%) of warfarin patients (n= 719) had a symptomatic recurrent VTE event

[b] Primary Efficacy Endpoint: Symptomatic recurrent VTE (i.e., the composite endpoint of DVT, non-fatal PE and fatal PE)

[c] Index PE refers to patients whose presenting diagnosis was PE (with or without concomitant DVT)

[d] Index DVT refers to patients whose presenting diagnosis was DVT only

Figure 14.3: Kaplan-Meier Cumulative Event Rate Estimates for Adjudicated Recurrent VTE (mITT analysis – on treatment)



16 HOW SUPPLIED/STORAGE AND HANDLING

SAVAYSA (edoxaban) is supplied as round shaped, film-coated, non-scored tablets containing edoxaban tosylate equivalent to 60, 30 or 15 mg of SAVAYSA, packaged in bottles and blisters.

			NDC 65597-xxx-yy					
			xxx	yy				
				Bottle of			Blister of	
Strength	Color	Deboss		30	90	500	10 x 10*	10 x 5**
15 mg	orange	DSC L15	201	30	-	-	-	-
30 mg	pink	DSC L30	202	30	90	50	10	05
60 mg	yellow	DSC L60	203	30	90	50	10	05

*10 blister cards of 10 counts **5 blister cards of 10 counts

Store at 20-25°C (68-77°F); excursions permitted to 15°-30°C (59°-86°F) *[see USP Controlled Room Temperature].*

Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

- they may bleed more easily, may bleed longer, or bruise more easily when treated with SAVAYSA
- to report any unusual bleeding immediately to their healthcare provider
- to take SAVAYSA exactly as prescribed
- to not discontinue SAVAYSA without talking to the healthcare provider who prescribed it
- to inform their healthcare providers that they are taking SAVAYSA before any surgery, medical, or dental procedure is scheduled
- to inform their healthcare providers and dentists if they plan to take, or are taking any prescription medications, over-the-counter drugs or herbal products
- to inform their healthcare provider immediately if they become pregnant or intend to become pregnant or are breastfeeding or intend to breastfeed during treatment with SAVAYSA
- that if a dose is missed, take SAVAYSA as soon as possible the same day, and resume the normal dosing schedule the following day. The dose should not be doubled to make up for a missing dose
- that if they are having neuraxial anesthesia or spinal puncture, advise patients to watch for signs and symptoms of spinal or epidural hematoma, such as back pain, tingling, numbness (especially in the lower limbs), muscle weakness, and stool or urine incontinence. If any of these symptoms occur, advise the patient to contact his or her physician immediately *[see Boxed Warning].*

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Parsippany, NJ 07054 USA

MEDICATION GUIDE

SAVAYSA (sa vaye´ sah)

(edoxaban) TABLETS

What is the most important information I should know about SAVAYSA?

For people who take SAVAYSA for nonvalvular atrial fibrillation (a type of irregular heartbeat):

People with atrial fibrillation are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. SAVAYSA lowers your chance of having a stroke by helping to prevent clots from forming.

- Your doctor should check your kidney function before you start taking SAVAYSA. People whose kidneys work really well should not receive SAVAYSA because it may not work well to prevent stroke.
- Do not stop taking SAVAYSA without first talking to the doctor who prescribed it for you. Stopping SAVAYSA increases your risk of having a stroke.

For all people who take SAVAYSA:

- **SAVAYSA can cause bleeding** which can be serious, and sometimes lead to death. This is because SAVAYSA is a blood thinner medicine that reduces blood clotting. While taking SAVAYSA you may bruise more easily and bleeding may take longer to stop. You should call your doctor or get medical help right away if you experience bleeding that is severe (for example, coughing up or vomiting blood) or bleeding that cannot be controlled.

  You may have a higher risk of bleeding if you take SAVAYSA and take other medicines that increase your risk of bleeding, including:

  - aspirin or aspirin containing products
  - long-term (chronic) use of non-steroidal anti-inflammatory drugs (NSAIDs)
  - long-term (chronic) use of blood thinner medicines, such as:
  - warfarin sodium (Coumadin®, Jantoven®)
  - any medicine that contains heparin
  - selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)
  - other medicines to prevent or treat blood clots

  Tell your doctor if you take any of these medicines. Ask your doctor or pharmacist if you are not sure if your medicine is one listed above.
- **SAVAYSA is not for people with mechanical heart valves or people who have moderate to severe narrowing (stenosis) of their mitral valve.**
- **Spinal or epidural blood clots (hematoma).** People who take a blood thinner medicine (anticoagulant) like SAVAYSA, and have medicine injected into their spinal and epidural area, or have a spinal puncture have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your risk of developing a spinal or epidural blood clot is higher if:
  - a thin tube called an epidural catheter is placed in your back to give you certain medicine
  - you take NSAIDs or a medicine to prevent blood from clotting
  - you have a history of difficult or repeated epidural or spinal punctures
  - you have a history of problems with your spine or have had surgery on your spine.

  If you take SAVAYSA and receive spinal anesthesia or have a spinal puncture, your doctor should watch you closely for symptoms of spinal or epidural blood clots. Tell your doctor right away if you have back pain, tingling, numbness (especially in your legs and feet), muscle weakness, loss of control of the bowels or bladder (incontinence).

See **"What are the possible side effects of SAVAYSA?"** for more information about side effects.

What is SAVAYSA?

SAVAYSA is a prescription medicine used to:

- reduce the risk of stroke and blood clots in people who have atrial fibrillation not caused by a heart valve problem.
- treat blood clots in the veins of your legs (deep vein thrombosis) or lungs (pulmonary embolism), after you have been treated with an injectable blood thinner medicine for 5 to 10 days.

It is not known if SAVAYSA is safe and effective in children.

Who should not take SAVAYSA?

Do not take SAVAYSA if you currently have certain types of abnormal bleeding.

What should I tell my doctor before taking SAVAYSA?

Before you take SAVAYSA, tell your doctor if you:

- have liver or kidney problems
- have ever had bleeding problems
- have a mechanical heart valve
- are pregnant or plan to become pregnant. It is not known if SAVAYSA will harm your unborn baby. Tell your doctor right away if you become pregnant during treatment with SAVAYSA.
- are breastfeeding or plan to breastfeed. It is not known if SAVAYSA passes into your breast milk. You and your doctor should decide if you will take SAVAYSA or breastfeed. You should not do both.

Tell all of your doctors and dentists that you are taking SAVAYSA. They should talk to the doctor who prescribed SAVAYSA for you, before you have **any** surgery, medical or dental procedure.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some of your other medicines may affect the way SAVAYSA works. Certain medicines may increase your risk of bleeding or stroke when taken with SAVAYSA. See **"What is the most important information I should know about SAVAYSA?"**

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take SAVAYSA?

- **Take SAVAYSA exactly as prescribed by your doctor.**
- Your doctor will decide how long you should take SAVAYSA. **Do not change your dose or stop taking SAVAYSA unless your doctor tells you to. If you are taking SAVAYSA for atrial fibrillation, stopping SAVAYSA may increase your risk of having a stroke.**
- You can take SAVAYSA with or without food.
- If you miss a dose of SAVAYSA, take it as soon as you remember on the same day. Take your next dose at your usual time the next day. Do not take more than one dose of SAVAYSA at the same time to make up for a missed dose.
- **Do not run out of SAVAYSA. Refill your prescription before you run out**.
- If you take too much SAVAYSA, go to the nearest hospital emergency room or call your doctor right away.
- Call your doctor right away if you fall or injure yourself, especially if you hit your head. Your doctor may need to check you.

What are the possible side effects of SAVAYSA?

SAVAYSA can cause serious side effects. See **"What is the most important information I should know about SAVAYSA?"**

Common side effects in people who take SAVAYSA include, bleeding and low red blood cell count (anemia).

Talk to your doctor if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SAVAYSA?

- Store SAVAYSA at room temperature between 68°F to 77°F (20°C to 25°C).

Keep SAVAYSA and all medicines out of the reach of children.

General information about the safe and effective use of SAVAYSA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SAVAYSA for a condition for which it was not prescribed. Do not give SAVAYSA to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about SAVAYSA that is written for health professionals.

For more information, call 1-877-437-7763 or go to www.savaysa.com.

What are the ingredients in SAVAYSA?

Active ingredient: edoxaban tosylate monohydrate

Inactive ingredients: mannitol, pregelatinized starch, crospovidone, hydroxypropyl cellulose, magnesium stearate, talc, and carnauba wax. The color coatings contain hypromellose, titanium dioxide, talc, polyethylene glycol 8000, iron oxide yellow (15 mg tablets and 60 mg tablets), and iron oxide red (15 mg tablets and 30 mg tablets).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Daiichi Sankyo Co., LTD.
Tokyo 103-8426
Japan

Distributed by:
Daiichi Sankyo, Inc.
Parsippany, NJ 07054 USA

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APPENDIX F. US PACKAGE INSERT FOR RIVAROXABAN (XARELTO)

XARELTO®

(rivaroxaban) tablets, for oral use

Revised: 03/2017
070441-170404

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XARELTO® (rivaroxaban) safely and effectively. See full prescribing information for XARELTO.

XARELTO (rivaroxaban) tablets, for oral use
Initial U.S. Approval: 2011

WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

See full prescribing information for complete boxed warning

(A) Premature discontinuation of XARELTO increases the risk of thrombotic events

Premature discontinuation of any oral anticoagulant, including XARELTO, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy (2.3, 2.7, 5.1, 14.1).

(B) Spinal/epidural hematoma

Epidural or spinal hematomas have occurred in patients treated with XARELTO who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis (5.2, 5.3, 6.2).

Monitor patients frequently for signs and symptoms of neurological impairment and if observed, treat urgently. Consider the benefits and risks before neuraxial intervention in patients who are or who need to be anticoagulated (5.3).

---------- RECENT MAJOR CHANGES ----------

Warnings and Precautions (5.2, 5.4)	05/2016
Warnings and Precautions (5.3)	08/2016

----------INDICATIONS AND USAGE ----------

XARELTO is a factor Xa inhibitor indicated:

- to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (1.1)
- for the treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), and for the reduction in the risk of recurrence of DVT and of PE (1.2, 1.3, 1.4)
- for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery (1.5)

XARELTO® (rivaroxaban) tablets

---------- DOSAGE AND ADMINISTRATION ----------

- Take 15 mg and 20 mg tablets with food; take 10 mg tablets with or without food (2.2)
- Nonvalvular Atrial Fibrillation:
  - o For patients with CrCl >50 mL/min: 20 mg orally, once daily **with the evening meal** (2.4)
  - o For patients with CrCl 15 - 50 mL/min: 15 mg orally, once daily **with the evening meal** (2.4)
- Treatment of DVT, PE, and Reduction in the Risk of Recurrence of DVT and of PE: 15 mg orally twice daily with food for the first 21 days for the initial treatment of acute DVT or PE. After the initial treatment period, 20 mg orally once daily with food for the remaining treatment and the long-term reduction in the risk of recurrence of DVT and of PE. (2.5)
- Prophylaxis of DVT Following Hip or Knee Replacement Surgery: 10 mg orally, once daily with or without food (2.6)

---------- DOSAGE FORMS AND STRENGTHS ----------

Tablets: 10 mg, 15 mg, and 20 mg (3)

---------- CONTRAINDICATIONS ----------

- Active pathological bleeding (4)
- Severe hypersensitivity reaction to XARELTO (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Risk of bleeding: XARELTO can cause serious and fatal bleeding. Promptly evaluate signs and symptoms of blood loss. (5.2)
- Pregnancy-related hemorrhage: Use XARELTO with caution in pregnant women due to the potential for obstetric hemorrhage and/or emergent delivery. Promptly evaluate signs and symptoms of blood loss. (5.7)
- Prosthetic heart valves: XARELTO use not recommended (5.8)

---------- ADVERSE REACTIONS ----------

The most common adverse reaction (>5%) was bleeding. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

---------- DRUG INTERACTIONS ----------

- Combined P-gp and strong CYP3A4 inhibitors and inducers: Avoid concomitant use (7.2, 7.3)
- Anticoagulants: Avoid concomitant use (7.4)

---------- USE IN SPECIFIC POPULATIONS ----------

- Nursing mothers: discontinue drug or discontinue nursing (8.3)
- Renal impairment: Avoid or adjust dose based on CrCl and Indication (8.7)
- Hepatic impairment: Avoid use in patients with Child-Pugh B and C hepatic impairment or with any degree of hepatic disease associated with coagulopathy (8.8)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

XARELTO® (rivaroxaban) tablets

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

A. Premature discontinuation of XARELTO increases the risk of thrombotic events

Premature discontinuation of any oral anticoagulant, including XARELTO, increases the risk of thrombotic events. If anticoagulation with XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.3, 2.7), Warnings and Precautions (5.1), and Clinical Studies (14.1)]*.

B. Spinal/epidural hematoma

Epidural or spinal hematomas have occurred in patients treated with XARELTO who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of XARELTO and neuraxial procedures is not known**

***[see Warnings and Precautions (5.2, 5.3) and Adverse Reactions (6.2)]*.**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions (5.3)]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

1.1 Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

XARELTO is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

There are limited data on the relative effectiveness of XARELTO and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled *[see Clinical Studies (14.1)]*.

1.2 Treatment of Deep Vein Thrombosis

XARELTO is indicated for the treatment of deep vein thrombosis (DVT).

1.3 Treatment of Pulmonary Embolism

XARELTO is indicated for the treatment of pulmonary embolism (PE).

1.4 Reduction in the Risk of Recurrence of Deep Vein Thrombosis and of Pulmonary Embolism

XARELTO is indicated for the reduction in the risk of recurrence of deep vein thrombosis and of pulmonary embolism following initial 6 months treatment for DVT and/or PE.

1.5 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

XARELTO is indicated for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Indication	Dosage	
Reduction in Risk of Stroke in Nonvalvular Atrial Fibrillation (2.4)	CrCl >50 mL/min:	20 mg once daily **with the evening meal**
	CrCl 15 to 50 mL/min:	15 mg once daily **with the evening meal**
Treatment of DVT (2.5)	15 mg twice daily with food, for first 21 days	
Treatment of PE (2.5)	**▼after 21 days, transition to ▼**	
	20 mg once daily with food, for remaining treatment	
Reduction in the Risk of Recurrence of DVT and of PE (2.5)	20 mg once daily with food	
Prophylaxis of DVT Following Hip or Knee Replacement Surgery (2.6)	Hip replacement:	10 mg once daily for 35 days
	Knee replacement:	10 mg once daily for 12 days

2.2 Important Food Effect Information

The 15 mg and 20 mg XARELTO tablets should be taken with food, while the 10 mg tablet can be taken with or without food *[see Clinical Pharmacology (12.3)]*.

In the nonvalvular atrial fibrillation efficacy study XARELTO was taken with the evening meal.

2.3 Switching to and from XARELTO

Switching from Warfarin to XARELTO - When switching patients from warfarin to XARELTO, discontinue warfarin and start XARELTO as soon as the International Normalized Ratio (INR) is below 3.0 to avoid periods of inadequate anticoagulation.

Switching from XARELTO to Warfarin - No clinical trial data are available to guide converting patients from XARELTO to warfarin. XARELTO affects INR, so INR measurements made during coadministration with warfarin may not be useful for determining the appropriate dose of warfarin. One approach is to discontinue XARELTO and begin both a parenteral anticoagulant and warfarin at the time the next dose of XARELTO would have been taken.

Switching from XARELTO to Anticoagulants other than Warfarin - For patients currently taking XARELTO and transitioning to an anticoagulant with rapid onset, discontinue XARELTO and give the first dose of the other anticoagulant (oral or parenteral) at the time that the next XARELTO dose would have been taken *[see Drug Interactions (7.4)]*.

Switching from Anticoagulants other than Warfarin to XARELTO - For patients currently receiving an anticoagulant other than warfarin, start XARELTO 0 to 2 hours prior to the next scheduled evening administration of the drug (e.g., low molecular weight heparin or non-warfarin oral anticoagulant) and omit administration of the other anticoagulant. For unfractionated heparin being administered by continuous infusion, stop the infusion and start XARELTO at the same time.

2.4 Nonvalvular Atrial Fibrillation

For patients with creatinine clearance (CrCl) >50 mL/min, the recommended dose of XARELTO is 20 mg taken orally once daily with the evening meal. For patients with CrCl 15 to 50 mL/min, the recommended dose is 15 mg once daily with the evening meal *[see Use in Specific Populations (8.7)]*.

2.5 Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE

The recommended dose of XARELTO for the initial treatment of acute DVT and/or PE is 15 mg taken orally twice daily with food for the first 21 days. After this initial treatment period, the recommended dose of XARELTO is 20 mg taken orally once daily with food, at approximately the same time each day. The recommended dose of XARELTO for reduction in the risk of recurrence of DVT or PE is 20 mg taken orally once daily with food at approximately the same time each day *[see Clinical Studies (14.2)]*.

2.6 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The recommended dose of XARELTO is 10 mg taken orally once daily with or without food. The initial dose should be taken 6 to 10 hours after surgery provided that hemostasis has been established *[see Dosage and Administration (2.7)]*.

- For patients undergoing hip replacement surgery, treatment duration of 35 days is recommended.
- For patients undergoing knee replacement surgery, treatment duration of 12 days is recommended.

2.7 Discontinuation for Surgery and other Interventions

If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, XARELTO should be stopped at least 24 hours before the procedure to reduce the risk of bleeding *[see Warnings and Precautions (5.2)]*. In deciding whether a procedure should be delayed until 24 hours after the last dose of XARELTO, the increased risk of bleeding should be weighed against the urgency of intervention. XARELTO should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established, noting that the time to onset of therapeutic effect is short *[see Warnings and Precautions (5.1)]*. If oral medication cannot be taken during or after surgical intervention, consider administering a parenteral anticoagulant.

2.8 Missed Dose

If a dose of XARELTO is not taken at the scheduled time, administer the dose as soon as possible on the same day as follows:

- For patients receiving 15 mg twice daily: The patient should take XARELTO immediately to ensure intake of 30 mg XARELTO per day. In this particular instance, two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.
- For patients receiving 20 mg, 15 mg or 10 mg once daily: The patient should take the missed XARELTO dose immediately.

2.9 Administration Options

For patients who are unable to swallow whole tablets, 10 mg, 15 mg or 20 mg XARELTO tablets may be crushed and mixed with applesauce immediately prior to use and administered orally. After the administration of a crushed XARELTO 15 mg or 20 mg tablet, the dose should be immediately followed by food *[see Dosage and Administration (2.2, 2.4, 2.5) and Clinical Pharmacology (12.3)]*.

Administration via nasogastric (NG) tube or gastric feeding tube: After confirming gastric placement of the tube, 10 mg, 15 mg or 20 mg XARELTO tablets may be crushed and suspended in 50 mL of water and administered via an NG tube or gastric feeding tube. Since rivaroxaban absorption is dependent on the site of drug release, avoid administration of XARELTO distal to the stomach which can result in reduced absorption and thereby, reduced drug exposure. After the administration of a crushed XARELTO 15 mg or 20 mg tablet, the dose should then be immediately followed by enteral feeding *[see Clinical Pharmacology (12.3)]*.

Crushed 10 mg, 15 mg or 20 mg XARELTO tablets are stable in water and in applesauce for up to 4 hours. An *in vitro* compatibility study indicated that there is no adsorption of rivaroxaban from a water suspension of a crushed XARELTO tablet to PVC or silicone nasogastric (NG) tubing.

XARELTO® (rivaroxaban) tablets

3 DOSAGE FORMS AND STRENGTHS

- 10 mg tablets: Round, light red, biconvex and film-coated with a triangle pointing down above a "10" marked on one side and "Xa" on the other side
- 15 mg tablets: Round, red, biconvex, and film-coated with a triangle pointing down above a "15" marked on one side and "Xa" on the other side
- 20 mg tablets: Triangle-shaped, dark red, and film-coated with a triangle pointing down above a "20" marked on one side and "Xa" on the other side

4 CONTRAINDICATIONS

XARELTO is contraindicated in patients with:

- active pathological bleeding *[see Warnings and Precautions (5.2)]*
- severe hypersensitivity reaction to XARELTO (e.g., anaphylactic reactions) *[see Adverse Reactions (6.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including XARELTO, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO to warfarin in clinical trials in atrial fibrillation patients. If XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.3, 2.7) and Clinical Studies (14.1)]*.

5.2 Risk of Bleeding

XARELTO increases the risk of bleeding and can cause serious or fatal bleeding. In deciding whether to prescribe XARELTO to patients at increased risk of bleeding, the risk of thrombotic events should be weighed against the risk of bleeding.

Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue XARELTO in patients with active pathological hemorrhage. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

Concomitant use of other drugs that impair hemostasis increases the risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, non-steroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions (7.4)]*, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors.

Concomitant use of drugs that are known combined P-gp and strong CYP3A4 inhibitors increases rivaroxaban exposure and may increase bleeding risk *[see Drug Interactions (7.2)]*.

Reversal of Anticoagulant Effect

A specific antidote for rivaroxaban is not available. Because of high plasma protein binding, rivaroxaban is not expected to be dialyzable *[see Clinical Pharmacology (12.3)]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. Partial reversal of prothrombin time prolongation has been seen after administration of prothrombin complex concentrates (PCCs) in healthy volunteers. The use of other procoagulant reversal agents like activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (rFVIIa) has not been evaluated.

5.3 Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis *[see Boxed Warning]*.

To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban *[see Clinical Pharmacology (12.3)]*. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

An indwelling epidural or intrathecal catheter should not be removed before at least 2 half-lives have elapsed (i.e., 18 hours in young patients aged 20 to 45 years and 26 hours in elderly patients aged 60 to 76 years), after the last administration of XARELTO *[see Clinical Pharmacology (12.3)]*. The next XARELTO dose should not be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of XARELTO for 24 hours.

Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, monitor frequently to detect any signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), bowel and/or bladder dysfunction. Instruct patients to immediately report if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

5.4 Use in Patients with Renal Impairment

Nonvalvular Atrial Fibrillation

Periodically assess renal function as clinically indicated (i.e., more frequently in situations in which renal function may decline) and adjust therapy accordingly *[see Dosage and Administration (2.4)]*. Consider dose adjustment or discontinuation of XARELTO in patients who develop acute renal failure while on XARELTO *[see Use in Specific Populations (8.7)]*.

Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE

Avoid the use of XARELTO in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population *[see Use in Specific Populations (8.7)]*.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

Avoid the use of XARELTO in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Patients who develop acute renal failure while on XARELTO should discontinue the treatment *[see Use in Specific Populations (8.7)]*.

5.5 Use in Patients with Hepatic Impairment

No clinical data are available for patients with severe hepatic impairment.

Avoid use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy since drug exposure and bleeding risk may be increased *[see Use in Specific Populations (8.8)]*.

5.6 Use with P-gp and Strong CYP3A4 Inhibitors or Inducers

Avoid concomitant use of XARELTO with known combined P-gp and strong CYP3A4 inhibitors *[see Drug Interactions (7.2)]*.

Avoid concomitant use of XARELTO with drugs that are known combined P-gp and strong CYP3A4 inducers *[see Drug Interactions (7.3)]*.

5.7 Risk of Pregnancy-Related Hemorrhage

In pregnant women, XARELTO should be used only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO cannot be monitored with standard laboratory testing nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).

5.8 Patients with Prosthetic Heart Valves

The safety and efficacy of XARELTO have not been studied in patients with prosthetic heart valves. Therefore, use of XARELTO is not recommended in these patients.

5.9 Acute PE in Hemodynamically Unstable Patients or Patients Who Require Thrombolysis or Pulmonary Embolectomy

Initiation of XARELTO is not recommended acutely as an alternative to unfractionated heparin in patients with pulmonary embolism who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

6 ADVERSE REACTIONS

The following adverse reactions are also discussed in other sections of the labeling:

- Increased risk of stroke after discontinuation in nonvalvular atrial fibrillation *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Bleeding risk *[see Warnings and Precautions (5.2, 5.4, 5.5, 5.6, 5.7)]*
- Spinal/epidural hematoma *[see Boxed Warning and Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During clinical development for the approved indications, 16326 patients were exposed to XARELTO. These included 7111 patients who received XARELTO 15 mg or 20 mg orally once daily for a mean of 19 months (5558 for 12 months and 2512 for 24 months) to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation (ROCKET AF); 4728 patients who received either XARELTO 15 mg orally twice daily for three weeks followed by 20 mg orally once daily (EINSTEIN DVT, EINSTEIN PE) or 20 mg orally once daily (EINSTEIN Extension) to treat DVT, PE, and to reduce the risk of recurrence of DVT and of PE; and 4487 patients who received XARELTO 10 mg orally once daily for prophylaxis of DVT following hip or knee replacement surgery (RECORD 1-3).

Hemorrhage

The most common adverse reactions with XARELTO were bleeding complications *[see Warnings and Precautions (5.2)]*.

Nonvalvular Atrial Fibrillation

In the ROCKET AF trial, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 4.3% for XARELTO vs. 3.1% for warfarin. The incidence of discontinuations for non-bleeding adverse events was similar in both treatment groups.

Table 1 shows the number of patients experiencing various types of bleeding events in the ROCKET AF trial.

Table 1: Bleeding Events in ROCKET AF*- On Treatment Plus 2 Days

Parameter	XARELTO N=7111 n (%/year)	Warfarin N=7125 n (%/year)	XARELTO vs. Warfarin HR (95% CI)
Major Bleeding†	395 (3.6)	386 (3.5)	1.04 (0.90, 1.20)
Intracranial Hemorrhage (ICH)‡	55 (0.5)	84 (0.7)	0.67 (0.47, 0.93)
Hemorrhagic Stroke§	36 (0.3)	58 (0.5)	0.63 (0.42, 0.96)
Other ICH	19 (0.2)	26 (0.2)	0.74 (0.41, 1.34)
Gastrointestinal (GI)¶	221 (2.0)	140 (1.2)	1.61 (1.30, 1.99)
Fatal Bleeding#	27 (0.2)	55 (0.5)	0.50 (0.31, 0.79)
ICH	24 (0.2)	42 (0.4)	0.58 (0.35, 0.96)
Non-intracranial	3 (0.0)	13 (0.1)	0.23 (0.07, 0.82)

Abbreviations: HR = Hazard Ratio, CI = Confidence interval, CRNM = Clinically Relevant Non-Major.

* Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories. These events occurred during treatment or within 2 days of stopping treatment.

† Defined as clinically overt bleeding associated with a decrease in hemoglobin of ≥2 g/dL, a transfusion of ≥2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome.

‡ Intracranial bleeding events included intraparenchymal, intraventricular, subdural, subarachnoid and/or epidural hematoma.

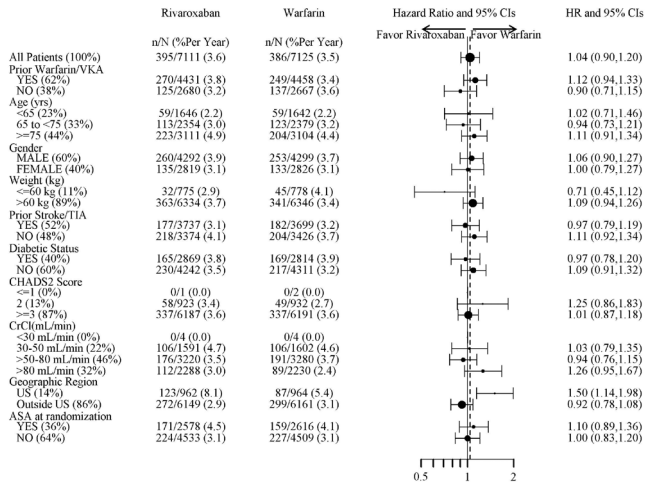
§ Hemorrhagic stroke in this table specifically refers to non-traumatic intraparenchymal and/or intraventricular hematoma in patients on treatment plus 2 days.

¶ Gastrointestinal bleeding events included upper GI, lower GI, and rectal bleeding.

Fatal bleeding is adjudicated death with the primary cause of death from bleeding.

Figure 1 shows the risk of major bleeding events across major subgroups.

Figure 1: Risk of Major Bleeding Events by Baseline Characteristics in ROCKET AF – On Treatment Plus 2 Days



Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified (diabetic status was not pre-specified in the subgroup, but was a criterion for the CHADS2 score). The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and to Reduce the Risk of Recurrence of DVT and of PE

EINSTEIN DVT and EINSTEIN PE Studies

In the pooled analysis of the EINSTEIN DVT and EINSTEIN PE clinical studies, the most frequent adverse reactions leading to permanent drug discontinuation were bleeding events, with XARELTO vs. enoxaparin/Vitamin K antagonist (VKA) incidence rates of 1.7% vs. 1.5%, respectively. The mean duration of treatment was 208 days for XARELTO-treated patients and 204 days for enoxaparin/VKA-treated patients.

Table 2 shows the number of patients experiencing major bleeding events in the pooled analysis of the EINSTEIN DVT and EINSTEIN PE studies.

Table 2: Bleeding Events* in the Pooled Analysis of EINSTEIN DVT and EINSTEIN PE Studies

Parameter	XARELTO† N=4130 n (%)	Enoxaparin/ VKA† N=4116 n (%)
Major bleeding event	40 (1.0)	72 (1.7)
Fatal bleeding	3 (<0.1)	8 (0.2)
Intracranial	2 (<0.1)	4 (<0.1)
Non-fatal critical organ bleeding	10 (0.2)	29 (0.7)
Intracranial‡	3 (<0.1)	10 (0.2)
Retroperitoneal‡	1 (<0.1)	8 (0.2)
Intraocular‡	3 (<0.1)	2 (<0.1)
Intra-articular‡	0	4 (<0.1)
Non-fatal non-critical organ bleeding§	27 (0.7)	37 (0.9)
Decrease in Hb ≥ 2 g/dL	28 (0.7)	42 (1.0)
Transfusion of ≥2 units of whole blood or packed red blood cells	18 (0.4)	25 (0.6)
Clinically relevant non-major bleeding	357 (8.6)	357 (8.7)
Any bleeding	1169 (28.3)	1153 (28.0)

* Bleeding event occurred after randomization and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.

† Treatment schedule in EINSTEIN DVT and EINSTEIN PE studies: XARELTO 15 mg twice daily for 3 weeks followed by 20 mg once daily; enoxaparin/VKA [enoxaparin: 1 mg/kg twice daily, VKA: individually titrated doses to achieve a target INR of 2.5 (range: 2.0-3.0)]

‡ Treatment-emergent major bleeding events with at least >2 subjects in any pooled treatment group

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§ Major bleeding which is not fatal or in a critical organ, but resulting in a decrease in Hb ≥ 2 g/dL and/or transfusion of ≥2 units of whole blood or packed red blood cells

EINSTEIN Extension Study

In the EINSTEIN Extension clinical study, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 1.8% for XARELTO vs. 0.2% for placebo treatment groups. The mean duration of treatment was 190 days for both XARELTO and placebo treatment groups.

Table 3 shows the number of patients experiencing bleeding events in the EINSTEIN Extension study.

Table 3: Bleeding Events* in EINSTEIN Extension Study

Parameter	XARELTO† 20 mg N=598 n (%)	Placebo† N=590 n (%)
Major bleeding event‡	4 (0.7)	0
Decrease in Hb ≥2 g/dL	4 (0.7)	0
Transfusion of ≥2 units of whole blood or packed red blood cells	2 (0.3)	0
Gastrointestinal	3 (0.5)	0
Menorrhagia	1 (0.2)	0
Clinically relevant non-major bleeding	32 (5.4)	7 (1.2)
Any bleeding	104 (17.4)	63 (10.7)

* Bleeding event occurred after the first dose and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.

† Treatment schedule: XARELTO 20 mg once daily; matched placebo once daily

‡ There were no fatal or critical organ bleeding events.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

In the RECORD clinical trials, the overall incidence rate of adverse reactions leading to permanent treatment discontinuation was 3.7% with XARELTO.

The rates of major bleeding events and any bleeding events observed in patients in the RECORD clinical trials are shown in Table 4.

Table 4: Bleeding Events* in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD 1-3)

	XARELTO 10 mg	Enoxaparin†
Total treated patients	**N=4487 n (%)**	**N=4524 n (%)**
Major bleeding event	14 (0.3)	9 (0.2)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	2 (<0.1)	3 (0.1)
Bleeding that required re-operation	7 (0.2)	5 (0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	4 (0.1)	1 (<0.1)
Any bleeding event‡	261 (5.8)	251 (5.6)
Hip Surgery Studies	**N=3281 n (%)**	**N=3298 n (%)**
Major bleeding event	7 (0.2)	3 (0.1)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	1 (<0.1)	1 (<0.1)
Bleeding that required re-operation	2 (0.1)	1 (<0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	3 (0.1)	1 (<0.1)
Any bleeding event‡	201 (6.1)	191 (5.8)
Knee Surgery Study	**N=1206 n (%)**	**N=1226 n (%)**
Major bleeding event	7 (0.6)	6 (0.5)
Fatal bleeding	0	0
Bleeding into a critical organ	1 (0.1)	2 (0.2)
Bleeding that required re-operation	5 (0.4)	4 (0.3)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	1 (0.1)	0
Any bleeding event‡	60 (5.0)	60 (4.9)

* Bleeding events occurring any time following the first dose of double-blind study medication (which may have been prior to administration of active drug) until two days after the last dose of double-blind study medication. Patients may have more than one event.
† Includes the placebo-controlled period for RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)
‡ Includes major bleeding events

Following XARELTO treatment, the majority of major bleeding complications (≥60%) occurred during the first week after surgery.

Other Adverse Reactions

Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in the EINSTEIN Extension study are shown in Table 5.

Table 5: Other Adverse Reactions* Reported by ≥1% of XARELTO-Treated Patients in EINSTEIN Extension Study

System Organ Class Preferred Term	XARELTO N=598 n (%)	Placebo N=590 n (%)
Gastrointestinal disorders		
Abdominal pain upper	10 (1.7)	1 (0.2)
Dyspepsia	8 (1.3)	4 (0.7)
Toothache	6 (1.0)	0
General disorders and administration site conditions		
Fatigue	6 (1.0)	3 (0.5)
Infections and infestations		
Sinusitis	7 (1.2)	3 (0.5)
Urinary tract infection	7 (1.2)	3 (0.5)
Musculoskeletal and connective tissue disorders		
Back pain	22 (3.7)	7 (1.2)
Osteoarthritis	10 (1.7)	5 (0.8)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	6 (1.0)	2 (0.3)

* Adverse reaction (with Relative Risk >1.5 for XARELTO versus placebo) occurred after the first dose and up to 2 days after the last dose of study drug. Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical adverse reactions, the patient is counted only once in a category. The same patient may appear in different categories.

Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in RECORD 1-3 studies are shown in Table 6.

Table 6: Other Adverse Drug Reactions* Reported by ≥1% of XARELTO-Treated Patients in RECORD 1-3 Studies

System/Organ Class Adverse Reaction	XARELTO 10 mg N=4487 n (%)	Enoxaparin† N=4524 n (%)
Injury, poisoning and procedural complications		
Wound secretion	125 (2.8)	89 (2.0)
Musculoskeletal and connective tissue disorders		
Pain in extremity	74 (1.7)	55 (1.2)
Muscle spasm	52 (1.2)	32 (0.7)
Nervous system disorders		
Syncope	55 (1.2)	32 (0.7)
Skin and subcutaneous tissue disorders		
Pruritus	96 (2.1)	79 (1.8)
Blister	63 (1.4)	40 (0.9)

* Adverse reaction occurring any time following the first dose of double-blind medication, which may have been prior to administration of active drug, until two days after the last dose of double-blind study medication
† Includes the placebo-controlled period of RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

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Other clinical trial experience: In an investigational study of acute medically ill patients being treated with XARELTO 10 mg tablets, cases of pulmonary hemorrhage and pulmonary hemorrhage with bronchiectasis were observed.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of rivaroxaban. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: agranulocytosis, thrombocytopenia
Gastrointestinal disorders: retroperitoneal hemorrhage
Hepatobiliary disorders: jaundice, cholestasis, hepatitis (including hepatocellular injury)
Immune system disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, angioedema
Nervous system disorders: cerebral hemorrhage, subdural hematoma, epidural hematoma, hemiparesis
Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

7 DRUG INTERACTIONS

7.1 General Inhibition and Induction Properties

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Combined P-gp and strong CYP3A4 inhibitors increase exposure to rivaroxaban and may increase the risk of bleeding. Combined P-gp and strong CYP3A4 inducers decrease exposure to rivaroxaban and may increase the risk of thromboembolic events.

7.2 Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems

Interaction with Combined P-gp and Strong CYP3A4 Inhibitors

Avoid concomitant administration of XARELTO with known combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole and ritonavir) *[see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)]*.

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggests that no precautions are necessary with concomitant administration with XARELTO as the change in exposure is unlikely to affect the bleeding risk *[see Clinical Pharmacology (12.3)]*.

Interaction with Combined P-gp and Moderate CYP3A4 Inhibitors in Patients with Renal Impairment

XARELTO should not be used in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A4 inhibitors (e.g., erythromycin) unless the potential benefit justifies the potential risk *[see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]*.

7.3 Drugs that Induce Cytochrome P450 3A4 Enzymes and Drug Transport Systems

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) *[see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)]*.

7.4 Anticoagulants and NSAIDs/Aspirin

Coadministration of enoxaparin, warfarin, aspirin, clopidogrel and chronic NSAID use may increase the risk of bleeding *[see Clinical Pharmacology (12.3)]*.

Avoid concurrent use of XARELTO with other anticoagulants due to increased bleeding risk unless benefit outweighs risk. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate or well-controlled studies of XARELTO in pregnant women, and dosing for pregnant women has not been established. Use XARELTO with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO cannot be reliably monitored with standard laboratory testing. Animal reproduction studies showed no increased risk of structural malformations, but increased post-implantation pregnancy loss occurred in rabbits. XARELTO should be used during pregnancy only if the potential benefit justifies the potential risk to mother and fetus *[see Warnings and Precautions (5.7)]*.

Rivaroxaban crosses the placenta in animals. Animal reproduction studies have shown pronounced maternal hemorrhagic complications in rats and an increased incidence of post-implantation pregnancy loss in rabbits.

Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weight) when pregnant rabbits were given oral doses of ≥10 mg/kg rivaroxaban during the period of organogenesis. This dose corresponds to about 4 times the human exposure of unbound drug, based on AUC comparisons at the highest recommended human dose of 20 mg/day. Fetal body weights decreased when pregnant rats were given oral doses of 120 mg/kg. This dose corresponds to about 14 times the human exposure of unbound drug.

8.2 Labor and Delivery

Safety and effectiveness of XARELTO during labor and delivery have not been studied in clinical trials. However, in animal studies maternal bleeding and maternal and fetal death occurred at the rivaroxaban dose of 40 mg/kg (about 6 times maximum human exposure of the unbound drug at the human dose of 20 mg/day).

8.3 Nursing Mothers

It is not known if rivaroxaban is excreted in human milk. Rivaroxaban and/or its metabolites were excreted into the milk of rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rivaroxaban, a decision should be made whether to discontinue nursing or discontinue XARELTO, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in the RECORD 1-3 clinical studies evaluating XARELTO, about 54% were 65 years and over, while about 15% were >75 years. In ROCKET AF, approximately 77% were 65 years and over and about 38% were >75 years. In the EINSTEIN DVT, PE and Extension clinical studies approximately 37% were 65 years and over and about 16% were >75 years. In clinical trials the efficacy of XARELTO in the elderly (65 years or older) was similar to that seen in patients younger than 65 years. Both thrombotic and bleeding event rates were higher in these older patients, but the risk-benefit profile was favorable in all age groups *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

8.6 Females of Reproductive Potential

Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

8.7 Renal Impairment

In pharmacokinetic studies, compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased by approximately 44 to 64% in subjects with renal impairment. Increases in pharmacodynamic effects were also observed *[see Clinical Pharmacology (12.3)]*.

Nonvalvular Atrial Fibrillation

In the ROCKET AF trial, patients with CrCl 30 to 50 mL/min were administered XARELTO 15 mg once daily resulting in serum concentrations of rivaroxaban and clinical outcomes similar to those in patients with better renal function administered XARELTO 20 mg once daily. Patients with CrCl 15 to 30 mL/min were not studied, but administration of XARELTO 15 mg once daily is also expected to result in serum concentrations of rivaroxaban similar to those in patients with normal renal function *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with XARELTO did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of XARELTO 15 mg once daily will result in concentrations of rivaroxaban and pharmacodynamic activity similar to those observed in the ROCKET AF study *[see Clinical Pharmacology (12.2, 12.3)]*. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ROCKET AF.

Treatment of DVT and/or PE, and Reduction in the Risk of Recurrence of DVT and of PE

In the EINSTEIN trials, patients with CrCl values <30 mL/min at screening were excluded from the studies. Avoid the use of XARELTO in patients with CrCl <30 mL/min.

Prophylaxis of DVT Following Hip or Knee Replacement Surgery

The combined analysis of the RECORD 1-3 clinical efficacy studies did not show an increase in bleeding risk for patients with CrCl 30 to 50 mL/min and reported a possible increase in total venous thromboemboli in this population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Avoid the use of XARELTO in patients with CrCl <30 mL/min.

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8.8 Hepatic Impairment

In a pharmacokinetic study, compared to healthy subjects with normal liver function, AUC increases of 127% were observed in subjects with moderate hepatic impairment (Child-Pugh B).

The safety or PK of XARELTO in patients with severe hepatic impairment (Child-Pugh C) has not been evaluated *[see Clinical Pharmacology (12.3)]*.

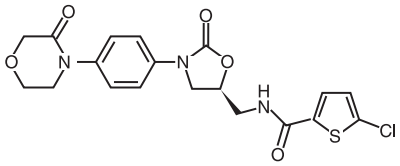
Avoid the use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy.

10 OVERDOSAGE

Overdose of XARELTO may lead to hemorrhage. Discontinue XARELTO and initiate appropriate therapy if bleeding complications associated with overdosage occur. A specific antidote for rivaroxaban is not available. Rivaroxaban systemic exposure is not further increased at single doses >50 mg due to limited absorption. The use of activated charcoal to reduce absorption in case of XARELTO overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not dialyzable *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*. Partial reversal of laboratory anticoagulation parameters may be achieved with use of plasma products.

11 DESCRIPTION

Rivaroxaban, a FXa inhibitor, is the active ingredient in XARELTO Tablets with the chemical name 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl) phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide. The molecular formula of rivaroxaban is $C_{19}H_{18}ClN_3O_5S$ and the molecular weight is 435.89. The structural formula is:



Rivaroxaban is a pure (*S*)-enantiomer. It is an odorless, non-hygroscopic, white to yellowish powder. Rivaroxaban is only slightly soluble in organic solvents (e.g., acetone, polyethylene glycol 400) and is practically insoluble in water and aqueous media.

Each XARELTO tablet contains 10 mg, 15 mg, or 20 mg of rivaroxaban. The inactive ingredients of XARELTO are: croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. Additionally, the proprietary film coating mixture used for XARELTO 10 mg tablets is Opadry® Pink and for XARELTO 15 mg tablets is Opadry® Red, both containing ferric oxide red, hypromellose, polyethylene glycol 3350, and titanium dioxide, and for XARELTO 20 mg tablets is Opadry® II Dark Red, containing ferric oxide red, polyethylene glycol 3350, polyvinyl alcohol (partially hydrolyzed), talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

XARELTO is a selective inhibitor of FXa. It does not require a cofactor (such as Anti-thrombin III) for activity. Rivaroxaban inhibits free FXa and prothrombinase activity. Rivaroxaban has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, rivaroxaban decreases thrombin generation.

12.2 Pharmacodynamics

Dose-dependent inhibition of FXa activity was observed in humans. Neoplastin® prothrombin time (PT), activated partial thromboplastin time (aPTT) and HepTest® are also prolonged dose-dependently. Anti-factor Xa activity is also influenced by rivaroxaban.

Specific Populations

Renal Impairment

The relationship between systemic exposure and pharmacodynamic activity of rivaroxaban was altered in subjects with renal impairment relative to healthy control subjects *[see Use in Specific Populations (8.7)]*.

Table 7: Percentage Increase in Rivaroxaban PK and PD Measures in Subjects with Renal Impairment Relative to Healthy Subjects from Clinical Pharmacology Studies

Measure	Parameter	Creatinine Clearance (mL/min)				
		50-79	30-49	15-29	ESRD (on dialysis)*	ESRD (post-dialysis)*
Exposure	AUC	44	52	64	47	56
FXa Inhibition	AUEC	50	86	100	49	33
PT Prolongation	AUEC	33	116	144	112	158

**Separate stand-alone study.*
PT = Prothrombin time; FXa = Coagulation factor Xa; AUC = Area under the plasma concentration-time curve; AUEC = Area under the effect-time curve

Hepatic Impairment
Anti-Factor Xa activity was similar in subjects with normal hepatic function and in mild hepatic impairment (Child-Pugh A class). There is no clear understanding of the impact of hepatic impairment beyond this degree on the coagulation cascade and its relationship to efficacy and safety.

12.3 Pharmacokinetics

Absorption
The absolute bioavailability of rivaroxaban is dose-dependent. For the 10 mg dose, it is estimated to be 80% to 100% and is not affected by food. XARELTO 10 mg tablets can be taken with or without food. For the 20 mg dose in the fasted state, the absolute bioavailability is approximately 66%. Coadministration of XARELTO with food increases the bioavailability of the 20 mg dose (mean AUC and C_{max} increasing by 39% and 76% respectively with food). XARELTO 15 mg and 20 mg tablets should be taken with food *[see Dosage and Administration (2.2)]*.

The maximum concentrations (C_{max}) of rivaroxaban appear 2 to 4 hours after tablet intake. The pharmacokinetics of rivaroxaban were not affected by drugs altering gastric pH. Coadministration of XARELTO (30 mg single dose) with the H_2-receptor antagonist ranitidine (150 mg twice daily), the antacid aluminum hydroxide/magnesium hydroxide (10 mL) or XARELTO (20 mg single dose) with the PPI omeprazole (40 mg once daily) did not show an effect on the bioavailability and exposure of rivaroxaban (see Figure 3).

Absorption of rivaroxaban is dependent on the site of drug release in the GI tract. A 29% and 56% decrease in AUC and C_{max} compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when drug is released in the distal small intestine, or ascending colon. Avoid administration of rivaroxaban distal to the stomach which can result in reduced absorption and related drug exposure.

In a study with 44 healthy subjects, both mean AUC and C_{max} values for 20 mg rivaroxaban administered orally as a crushed tablet mixed in applesauce were comparable to that after the whole tablet. However, for the crushed tablet suspended in water and administered via an NG tube followed by a liquid meal, only mean AUC was comparable to that after the whole tablet, and C_{max} was 18% lower.

Distribution
Plasma protein binding of rivaroxaban in human plasma is approximately 92% to 95%, with albumin being the main binding component. The steady-state volume of distribution in healthy subjects is approximately 50 L.

Metabolism
Approximately 51% of an orally administered [^{14}C]-rivaroxaban dose was recovered as inactive metabolites in urine (30%) and feces (21%). Oxidative degradation catalyzed by CYP3A4/5 and CYP2J2 and hydrolysis are the major sites of biotransformation. Unchanged rivaroxaban was the predominant moiety in plasma with no major or active circulating metabolites.

Excretion
In a Phase 1 study, following the administration of [^{14}C]-rivaroxaban, approximately one-third (36%) was recovered as unchanged drug in the urine and 7% was recovered as unchanged drug in feces. Unchanged drug is excreted into urine, mainly via active tubular secretion and to a lesser extent via glomerular filtration (approximate 5:1 ratio). Rivaroxaban is a substrate of the efflux transporter proteins P-gp and ABCG2 (also abbreviated Bcrp). Rivaroxaban's affinity for influx transporter proteins is unknown.

Rivaroxaban is a low-clearance drug, with a systemic clearance of approximately 10 L/hr in healthy volunteers following intravenous administration. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

Specific Populations
The effects of level of renal impairment, age, body weight, and level of hepatic impairment on the pharmacokinetics of rivaroxaban are summarized in Figure 2.

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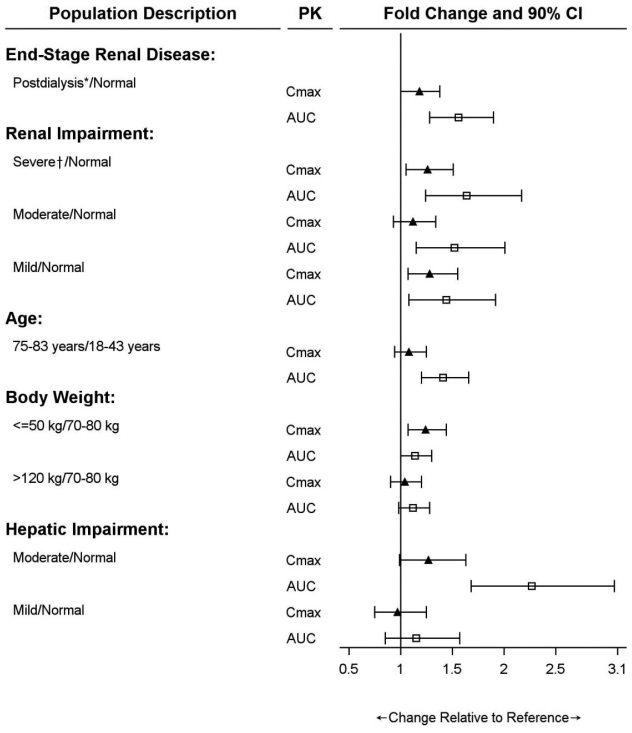
Figure 2: Effect of Specific Populations on the Pharmacokinetics of Rivaroxaban



* ESRD subjects maintained with chronic and stable hemodialysis; reported PK findings are following single dose of rivaroxaban post hemodialysis.
† Creatinine clearance 15 to 29 mL/min.

Gender
Gender did not influence the pharmacokinetics or pharmacodynamics of XARELTO.

Race
Healthy Japanese subjects were found to have 20 to 40% on average higher exposures compared to other ethnicities including Chinese. However, these differences in exposure are reduced when values are corrected for body weight.

Elderly
The terminal elimination half-life is 11 to 13 hours in the elderly subjects aged 60 to 76 years *[see Use in Specific Populations (8.5)]*.

Renal Impairment
The safety and pharmacokinetics of single-dose XARELTO (10 mg) were evaluated in a study in healthy subjects [CrCl ≥80 mL/min (n=8)] and in subjects with varying degrees of renal impairment (see Figure 2). Compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased in subjects with renal impairment. Increases in pharmacodynamic effects were also observed *[see Use in Specific Populations (8.7)]*.

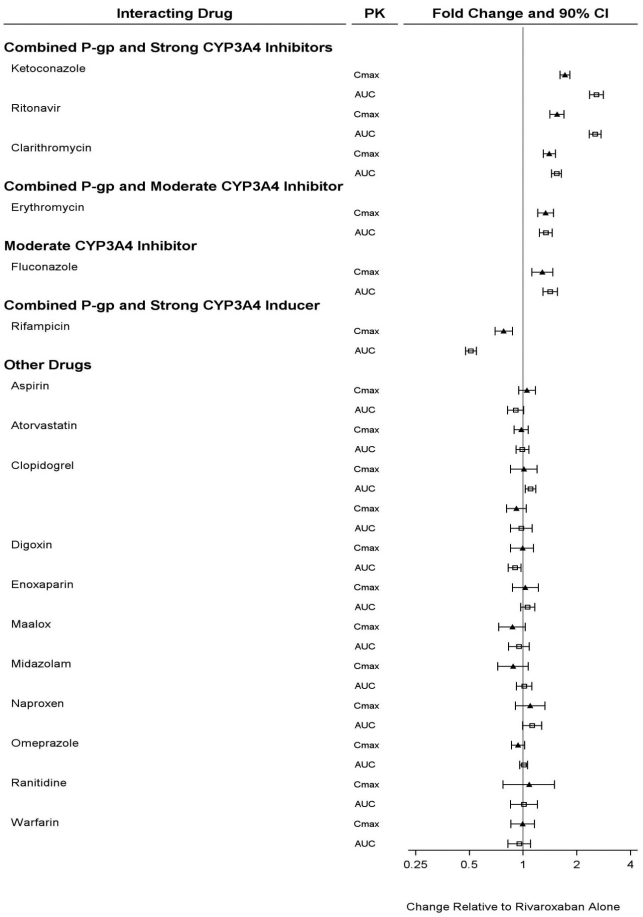
Hemodialysis in ESRD subjects: Systemic exposure to rivaroxaban administered as a single 15 mg dose in ESRD subjects dosed 3 hours after the completion of a 4-hour hemodialysis session (post-dialysis) is 56% higher when compared to subjects with normal renal function (see Table 7). The systemic exposure to rivaroxaban administered 2 hours prior to a 4-hour hemodialysis session with a dialysate flow rate of 600 mL/min and a blood flow rate in the range of 320 to 400 mL/min is 47% higher compared to those with normal renal function. The extent of the increase is similar to the increase in patients with CrCl 15 to 50 mL/min taking XARELTO 15 mg. Hemodialysis had no significant impact on rivaroxaban exposure. Protein binding was similar (86% to 89%) in healthy controls and ESRD subjects in this study.

Hepatic Impairment
The safety and pharmacokinetics of single-dose XARELTO (10 mg) were evaluated in a study in healthy subjects (n=16) and subjects with varying degrees of hepatic impairment (see Figure 2). No patients with severe hepatic impairment (Child-Pugh C) were studied. Compared to healthy subjects with normal liver function, significant increases in rivaroxaban exposure were observed in subjects with moderate hepatic impairment (Child-Pugh B) (see Figure 2). Increases in pharmacodynamic effects were also observed *[see Use in Specific Populations (8.8)]*.

Drug Interactions
In vitro studies indicate that rivaroxaban neither inhibits the major cytochrome P450 enzymes CYP1A2, 2C8, 2C9, 2C19, 2D6, 2J2, and 3A4 nor induces CYP1A2, 2B6, 2C19, or 3A4. *In vitro* data also indicates a low rivaroxaban inhibitory potential for P-gp and ABCG2 transporters.

The effects of coadministered drugs on the pharmacokinetics of rivaroxaban exposure are summarized in Figure 3 *[see Drug Interactions (7) for dosing recommendations].*

Figure 3: Effect of Coadministered Drugs on the Pharmacokinetics of Rivaroxaban



Anticoagulants
In a drug interaction study, single doses of enoxaparin (40 mg subcutaneous) and XARELTO (10 mg) given concomitantly resulted in an additive effect on anti-factor Xa activity. In another study, single doses of warfarin (15 mg) and XARELTO (5 mg) resulted in an additive effect on factor Xa inhibition and PT. Neither enoxaparin nor warfarin affected the pharmacokinetics of rivaroxaban (see Figure 3).

NSAIDs/Aspirin
In ROCKET AF, concomitant aspirin use (almost exclusively at a dose of 100 mg or less) during the double-blind phase was identified as an independent risk factor for major bleeding. NSAIDs are known to increase bleeding, and bleeding risk may be increased when NSAIDs are used concomitantly with XARELTO. Neither naproxen nor aspirin affected the pharmacokinetics of rivaroxaban (see Figure 3).

Clopidogrel
In two drug interaction studies where clopidogrel (300 mg loading dose followed by 75 mg daily maintenance dose) and XARELTO (15 mg single dose) were coadministered in healthy subjects, an increase in bleeding time to 45 minutes was observed in approximately 45% and 30% of subjects in these studies, respectively. The change in bleeding time was approximately twice the maximum increase seen with either drug alone. There was no change in the pharmacokinetics of either drug.

Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems
In a pharmacokinetic trial, XARELTO was administered as a single dose in subjects with mild (CrCl = 50 to 79 mL/min) or moderate renal impairment (CrCl = 30 to 49 mL/min) receiving multiple doses of erythromycin (a combined P-gp and moderate CYP3A4 inhibitor). Compared to XARELTO administered alone in subjects with normal renal function (CrCl >80 mL/min), subjects with mild and moderate renal impairment concomitantly receiving erythromycin reported a 76% and 99% increase in AUC_{inf} and a 56% and 64% increase in C_{max}, respectively. Similar trends in pharmacodynamic effects were also observed.

12.6 QT/QTc Prolongation
In a thorough QT study in healthy men and women aged 50 years and older, no QTc prolonging effects were observed for XARELTO (15 mg and 45 mg, single-dose).

13 NON-CLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Rivaroxaban was not carcinogenic when administered by oral gavage to mice or rats for up to 2 years. The systemic exposures (AUCs) of unbound rivaroxaban in male and female mice at the highest dose tested (60 mg/kg/day) were 1- and 2-times, respectively, the human exposure of unbound drug at the human dose of 20 mg/day. Systemic exposures of unbound drug in male and female rats at the highest dose tested (60 mg/kg/day) were 2- and 4-times, respectively, the human exposure.

Rivaroxaban was not mutagenic in bacteria (Ames-Test) or clastogenic in V79 Chinese hamster lung cells *in vitro* or in the mouse micronucleus test *in vivo*.

No impairment of fertility was observed in male or female rats when given up to 200 mg/kg/day of rivaroxaban orally. This dose resulted in exposure levels, based on the unbound AUC, at least 13 times the exposure in humans given 20 mg rivaroxaban daily.

14 CLINICAL STUDIES
14.1 Stroke Prevention in Nonvalvular Atrial Fibrillation
The evidence for the efficacy and safety of XARELTO was derived from ROCKET AF, a multi-national, double-blind study comparing XARELTO (at a dose of 20 mg once daily with the evening meal in patients with CrCl >50 mL/min and 15 mg once daily with the evening meal in patients with CrCl 30 to 50 mL/min) to warfarin (titrated to INR 2.0 to 3.0) to reduce the risk of stroke and non-central nervous system (CNS) systemic embolism in patients with nonvalvular atrial fibrillation (AF). Patients had to have one or more of the following additional risk factors for stroke:

- a prior stroke (ischemic or unknown type), transient ischemic attack (TIA) or non-CNS systemic embolism, or
- 2 or more of the following risk factors:
  - o age ≥75 years,
  - o hypertension,
  - o heart failure or left ventricular ejection fraction ≤35%, or
  - o diabetes mellitus

ROCKET AF was a non-inferiority study designed to demonstrate that XARELTO preserved more than 50% of warfarin's effect on stroke and non-CNS systemic embolism as established by previous placebo-controlled studies of warfarin in atrial fibrillation.

A total of 14264 patients were randomized and followed on study treatment for a median of 590 days. The mean age was 71 years and the mean $CHADS_2$ score was 3.5. The population was 60% male, 83% Caucasian, 13% Asian and 1.3% Black. There was a history of stroke, TIA, or non-CNS systemic embolism in 55% of patients, and 38% of patients had not taken a vitamin K antagonist (VKA) within 6 weeks at time of screening. Concomitant diseases of patients in this study included hypertension 91%, diabetes 40%, congestive heart failure 63%, and prior myocardial infarction 17%. At baseline, 37% of patients were on aspirin (almost exclusively at a dose of 100 mg or less) and few patients were on clopidogrel. Patients were enrolled in Eastern Europe (39%); North America (19%); Asia, Australia, and New Zealand (15%); Western Europe (15%); and Latin America (13%). Patients randomized to warfarin had a mean percentage of time in the INR target range of 2.0 to 3.0 of 55%, lower during the first few months of the study.

In ROCKET AF, XARELTO was demonstrated non-inferior to warfarin for the primary composite endpoint of time to first occurrence of stroke (any type) or non-CNS systemic embolism [HR (95% CI): 0.88 (0.74, 1.03)], but superiority to warfarin was not demonstrated. There is insufficient experience to determine how XARELTO and warfarin compare when warfarin therapy is well-controlled.

Table 8 displays the overall results for the primary composite endpoint and its components.

Table 8: Primary Composite Endpoint Results in ROCKET AF Study (Intent-to-Treat Population)

	XARELTO		Warfarin		XARELTO vs. Warfarin
Event	**N=7081 n (%)**	**Event Rate (per 100 Pt-yrs)**	**N=7090 n (%)**	**Event Rate (per 100 Pt-yrs)**	**Hazard Ratio (95% CI)**
Primary Composite Endpoint*	269 (3.8)	2.1	306 (4.3)	2.4	0.88 (0.74, 1.03)
Stroke	253 (3.6)	2.0	281 (4.0)	2.2	
Hemorrhagic Stroke†	33 (0.5)	0.3	57 (0.8)	0.4	
Ischemic Stroke	206 (2.9)	1.6	208 (2.9)	1.6	
Unknown Stroke Type	19 (0.3)	0.2	18 (0.3)	0.1	
Non-CNS Systemic Embolism	20 (0.3)	0.2	27 (0.4)	0.2	

* The primary endpoint was the time to first occurrence of stroke (any type) or non-CNS systemic embolism. Data are shown for all randomized patients followed to site notification that the study would end.

† Defined as primary hemorrhagic strokes confirmed by adjudication in all randomized patients followed up to site notification

Figure 4 is a plot of the time from randomization to the occurrence of the first primary endpoint event in the two treatment arms.

Figure 4: Time to First Occurrence of Stroke (any type) or Non-CNS Systemic Embolism by Treatment Group (Intent-to-Treat Population)

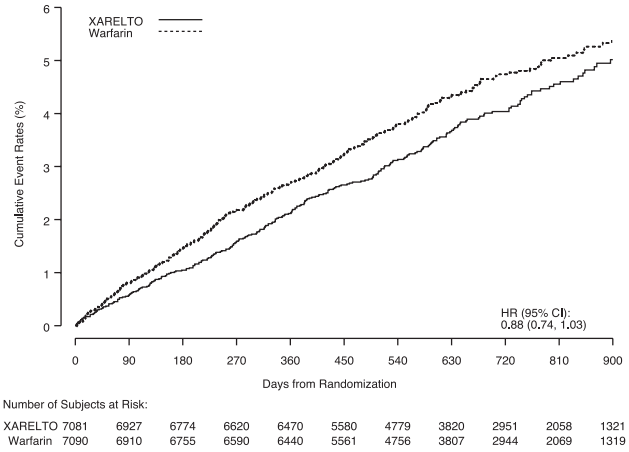
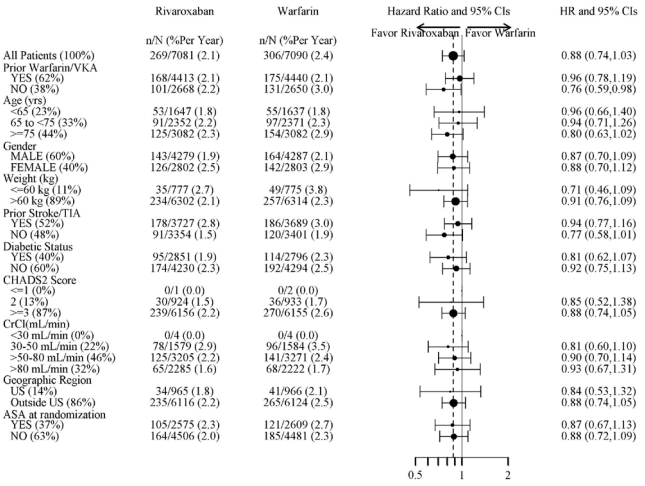


Figure 5 shows the risk of stroke or non-CNS systemic embolism across major subgroups.

Figure 5: Risk of Stroke or Non-CNS Systemic Embolism by Baseline Characteristics in ROCKET AF* (Intent-to-Treat Population)



* Data are shown for all randomized patients followed to site notification that the study would end.

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Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified (diabetic status was not pre-specified in the subgroup, but was a criterion for the CHADS2 score). The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

The efficacy of XARELTO was generally consistent across major subgroups.

The protocol for ROCKET AF did not stipulate anticoagulation after study drug discontinuation, but warfarin patients who completed the study were generally maintained on warfarin. XARELTO patients were generally switched to warfarin without a period of coadministration of warfarin and XARELTO, so that they were not adequately anticoagulated after stopping XARELTO until attaining a therapeutic INR. During the 28 days following the end of the study, there were 22 strokes in the 4637 patients taking XARELTO vs. 6 in the 4691 patients taking warfarin.

Few patients in ROCKET AF underwent electrical cardioversion for atrial fibrillation. The utility of XARELTO for preventing post-cardioversion stroke and systemic embolism is unknown.

14.2 Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE

EINSTEIN Deep Vein Thrombosis and EINSTEIN Pulmonary Embolism Studies

XARELTO for the treatment of DVT and/or PE and for the reduction in the risk of recurrence of DVT and of PE was studied in EINSTEIN DVT and EINSTEIN PE, multi-national, open-label, non-inferiority studies comparing XARELTO (at an initial dose of 15 mg twice daily with food for the first three weeks, followed by XARELTO 20 mg once daily with food) to enoxaparin 1 mg/kg twice daily for at least five days with VKA and then continued with VKA only after the target INR (2.0-3.0) was reached. Patients who required thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent and patients with creatinine clearance <30 mL/min, significant liver disease, or active bleeding were excluded from the studies. The intended treatment duration was 3, 6, or 12 months based on investigator's assessment prior to randomization.

A total of 8281 (3449 in EINSTEIN DVT and 4832 in EINSTEIN PE) patients were randomized and followed on study treatment for a mean of 208 days in the XARELTO group and 204 days in the enoxaparin/VKA group. The mean age was approximately 57 years. The population was 55% male, 70% Caucasian, 9% Asian and about 3% Black. About 73% and 92% of XARELTO-treated patients in the EINSTEIN DVT and EINSTEIN PE studies, respectively, received initial parenteral anticoagulant treatment for a median duration of 2 days. Enoxaparin/VKA-treated patients in the EINSTEIN DVT and EINSTEIN PE studies received initial parenteral anticoagulant treatment for a median duration of 8 days. Aspirin was taken as on treatment concomitant antithrombotic medication by approximately 12% of patients in both treatment groups. Patients randomized to VKA had an unadjusted mean percentage of time in the INR target range of 2.0 to 3.0 of 58% in EINSTEIN DVT study and 60% in EINSTEIN PE study, with the lower values occurring during the first month of the study.

In the EINSTEIN DVT and EINSTEIN PE studies, 49% of patients had an idiopathic DVT/PE at baseline. Other risk factors included previous episode of DVT/PE (19%), recent surgery or trauma (18%), immobilization (16%), use of estrogen-containing drug (8%), known thrombophilic conditions (6%), or active cancer (5%).

In the EINSTEIN DVT and EINSTEIN PE studies, XARELTO was demonstrated to be non-inferior to enoxaparin/VKA for the primary composite endpoint of time to first occurrence of recurrent DVT or non-fatal or fatal PE [EINSTEIN DVT HR (95% CI): 0.68 (0.44, 1.04); EINSTEIN PE HR (95% CI): 1.12 (0.75, 1.68)]. In each study the conclusion of non-inferiority was based on the upper limit of the 95% confidence interval for the hazard ratio being less than 2.0.

Table 9 displays the overall results for the primary composite endpoint and its components for EINSTEIN DVT and EINSTEIN PE studies.

Table 9: Primary Composite Endpoint Results* in EINSTEIN DVT and EINSTEIN PE Studies – Intent-to-Treat Population

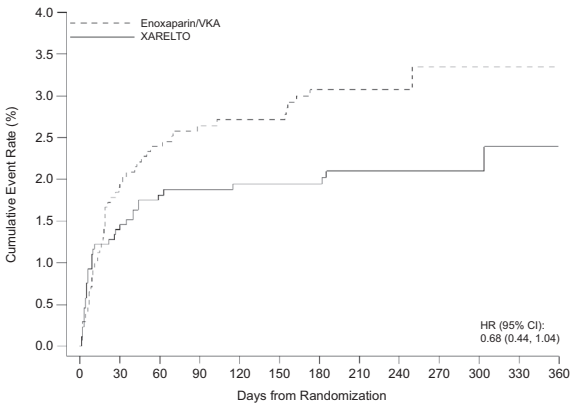
Event	XARELTO 20 mg†	Enoxaparin/ VKA†	XARELTO vs. Enoxaparin/VKA Hazard Ratio (95% CI)
EINSTEIN DVT Study	**N=1731 n (%)**	**N=1718 n (%)**	
Primary Composite Endpoint	36 (2.1)	51 (3.0)	0.68 (0.44, 1.04)
Death (PE)	1 (<0.1)	0	
Death (PE cannot be excluded)	3 (0.2)	6 (0.3)	
Symptomatic PE and DVT	1 (<0.1)	0	
Symptomatic recurrent PE only	20 (1.2)	18 (1.0)	
Symptomatic recurrent DVT only	14 (0.8)	28 (1.6)	
EINSTEIN PE Study	**N=2419 n (%)**	**N=2413 n (%)**	
Primary Composite Endpoint	50 (2.1)	44 (1.8)	1.12 (0.75, 1.68)
Death (PE)	3 (0.1)	1 (<0.1)	
Death (PE cannot be excluded)	8 (0.3)	6 (0.2)	
Symptomatic PE and DVT	0	2 (<0.1)	
Symptomatic recurrent PE only	23 (1.0)	20 (0.8)	
Symptomatic recurrent DVT only	18 (0.7)	17 (0.7)	

* For the primary efficacy analysis, all confirmed events were considered from randomization up to the end of intended treatment duration (3, 6 or 12 months) irrespective of the actual treatment duration. If the same patient had several events, the patient may have been counted for several components.

† Treatment schedule in EINSTEIN DVT and EINSTEIN PE studies: XARELTO 15 mg twice daily for 3 weeks followed by 20 mg once daily; enoxaparin/ VKA [enoxaparin: 1 mg/kg twice daily, VKA: individually titrated doses to achieve a target INR of 2.5 (range: 2.0-3.0)]

Figures 6 and 7 are plots of the time from randomization to the occurrence of the first primary efficacy endpoint event in the two treatment groups in EINSTEIN DVT and EINSTEIN PE studies, respectively.

Figure 6: Time to First Occurrence of the Composite of Recurrent DVT or Non-fatal or Fatal PE by Treatment Group (Intent-to-Treat Population) – EINSTEIN DVT Study



Number of Patients at Risk

Enoxaparin/VKA (N= 1718)	1616	1581	1565	1368	1358	1301	380	362	342	325	297	264
XARELTO (N= 1731)	1668	1648	1635	1424	1412	1369	400	369	364	345	309	266

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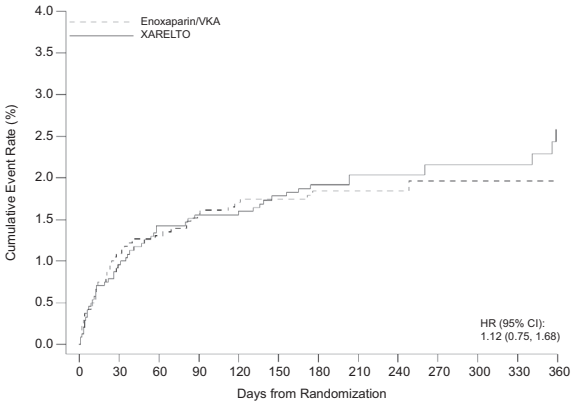
Figure 7: Time to First Occurrence of the Composite of Recurrent DVT or Non-fatal or Fatal PE by Treatment Group (Intent-to-Treat Population) – EINSTEIN PE Study



Number of Patients at Risk

Enoxaparin/VKA (N= 2413)	2316	2295	2280	2155	2146	2113	835	787	773	746	722	675
XARELTO (N= 2419)	2350	2321	2311	2180	2167	2133	837	794	785	757	725	672

EINSTEIN Extension Study

XARELTO for reduction in the risk of recurrence of DVT and of PE was studied in the EINSTEIN Extension study, a multi-national, double-blind, superiority study comparing XARELTO (20 mg once daily with food) to placebo in patients who had completed 6 to 14 months of treatment for DVT and/or PE following the acute event. The intended treatment duration was 6 or 12 months based on investigator's assessment prior to randomization.

A total of 1196 patients were randomized and followed on study treatment for a mean of 190 days for both XARELTO and placebo treatment groups. The mean age was approximately 58 years. The population was 58% male, 78% Caucasian, 8% Asian and about 2% Black. Aspirin was taken as on-treatment concomitant antithrombotic medication by approximately 12% of patients in both treatment groups. In the EINSTEIN Extension study about 60% of patients had a history of proximal index DVT without PE event and 29% of patients had a PE without symptomatic DVT event. About 59% of patients had an idiopathic DVT/PE. Other risk factors included previous episode of DVT/PE (16%), immobilization (14%), known thrombophilic conditions (8%), or active cancer (5%).

In the EINSTEIN Extension study XARELTO was demonstrated to be superior to placebo for the primary composite endpoint of time to first occurrence of recurrent DVT or non-fatal or fatal PE [HR (95% CI): 0.18 (0.09, 0.39)].

Table 10 displays the overall results for the primary composite endpoint and its components.

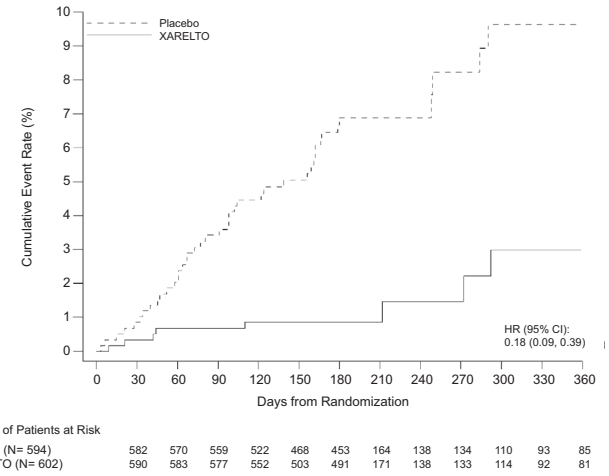
Table 10: Primary Composite Endpoint Results* in EINSTEIN Extension Study – Intent-to-Treat Population

Event	XARELTO 20 mg N=602 n (%)	Placebo N=594 n (%)	XARELTO vs. Placebo Hazard Ratio (95% CI)
Primary Composite Endpoint	8 (1.3)	42 (7.1)	0.18 (0.09, 0.39) p-value = <0.0001
Death (PE)	0	1 (0.2)	
Death (PE cannot be excluded)	1 (0.2)	0	
Symptomatic recurrent PE	2 (0.3)	13 (2.2)	
Symptomatic recurrent DVT	5 (0.8)	31 (5.2)	

* For the primary efficacy analysis, all confirmed events were considered from randomization up to the end of intended treatment duration (6 or 12 months) irrespective of the actual treatment duration.

Figure 8 is a plot of the time from randomization to the occurrence of the first primary efficacy endpoint event in the two treatment groups.

Figure 8: Time to First Occurrence of the Composite of Recurrent DVT or Non-fatal or Fatal PE by Treatment Group (Intent-to-Treat Population) – EINSTEIN Extension Study



14.3 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

XARELTO was studied in 9011 patients (4487 XARELTO-treated, 4524 enoxaparin-treated patients) in the RECORD 1, 2, and 3 studies.

The two randomized, double-blind, clinical studies (RECORD 1 and 2) in patients undergoing elective total hip replacement surgery compared XARELTO 10 mg once daily starting at least 6 to 8 hours (about 90% of patients dosed 6 to 10 hours) after wound closure versus enoxaparin 40 mg once daily started 12 hours preoperatively. In RECORD 1 and 2, a total of 6727 patients were randomized and 6579 received study drug. The mean age [± standard deviation (SD)] was 63 ± 12.2 (range 18 to 93) years with 49% of patients ≥65 years and 55% of patients were female. More than 82% of patients were White, 7% were Asian, and less than 2% were Black. The studies excluded patients undergoing staged bilateral total hip replacement, patients with severe renal impairment defined as an estimated creatinine clearance <30 mL/min, or patients with significant liver disease (hepatitis or cirrhosis). In RECORD 1, the mean exposure duration (± SD) to active XARELTO and enoxaparin was 33.3 ± 7.0 and 33.6 ± 8.3 days, respectively. In RECORD 2, the mean exposure duration to active XARELTO and enoxaparin was 33.5 ± 6.9 and 12.4 ± 2.9 days, respectively. After Day 13, oral placebo was continued in the enoxaparin group for the remainder of the double-blind study duration. The efficacy data for RECORD 1 and 2 are provided in Table 11.

Table 11: Summary of Key Efficacy Analysis Results for Patients Undergoing Total Hip Replacement Surgery - Modified Intent-to-Treat Population

	RECORD 1			RECORD 2		
Treatment Dosage and Duration	**XARELTO 10 mg once daily**	**Enoxaparin 40 mg once daily**	**RRR*, p-value**	**XARELTO 10 mg once daily**	**Enoxaparin† 40 mg once daily**	**RRR*, p-value**
Number of Patients	**N=1513**	**N=1473**		**N=834**	**N=835**	
Total VTE	17 (1.1%)	57 (3.9%)	71% (95% CI: 50, 83), p<0.001	17 (2.0%)	70 (8.4%)	76% (95% CI: 59, 86), p<0.001
Components of Total VTE						
Proximal DVT	1 (0.1%)	31 (2.1%)		5 (0.6%)	40 (4.8%)	
Distal DVT	12 (0.8%)	26 (1.8%)		11 (1.3%)	43 (5.2%)	
Non-fatal PE	3 (0.2%)	1 (0.1%)		1 (0.1%)	4 (0.5%)	
Death (any cause)	4 (0.3%)	4 (0.3%)		2 (0.2%)	4 (0.5%)	
Number of Patients	**N=1600**	**N=1587**		**N=928**	**N=929**	
Major VTE‡	3 (0.2%)	33 (2.1%)	91% (95% CI: 71, 97), p<0.001	6 (0.7%)	45 (4.8%)	87% (95% CI: 69, 94), p<0.001
Number of Patients	**N=2103**	**N=2119**		**N=1178**	**N=1179**	
Symptomatic VTE	5 (0.2%)	11 (0.5%)		3 (0.3%)	15 (1.3%)	

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* Relative Risk Reduction; CI = confidence interval
† Includes the placebo-controlled period of RECORD 2
‡ Proximal DVT, nonfatal PE or VTE-related death

One randomized, double-blind, clinical study (RECORD 3) in patients undergoing elective total knee replacement surgery compared XARELTO 10 mg once daily started at least 6 to 8 hours (about 90% of patients dosed 6 to 10 hours) after wound closure versus enoxaparin. In RECORD 3, the enoxaparin regimen was 40 mg once daily started 12 hours preoperatively. The mean age (± SD) of patients in the study was 68 ± 9.0 (range 28 to 91) years with 66% of patients ≥65 years. Sixty-eight percent (68%) of patients were female. Eighty-one percent (81%) of patients were White, less than 7% were Asian, and less than 2% were Black. The study excluded patients with severe renal impairment defined as an estimated creatinine clearance <30 mL/min or patients with significant liver disease (hepatitis or cirrhosis). The mean exposure duration (± SD) to active XARELTO and enoxaparin was 11.9 ± 2.3 and 12.5 ± 3.0 days, respectively. The efficacy data are provided in Table 12.

Table 12: Summary of Key Efficacy Analysis Results for Patients Undergoing Total Knee Replacement Surgery - Modified Intent-to-Treat Population

	RECORD 3		
Treatment Dosage and Duration	**XARELTO 10 mg once daily**	**Enoxaparin 40 mg once daily**	**RRR*, p-value**
Number of Patients	**N=813**	**N=871**	
Total VTE	79 (9.7%)	164 (18.8%)	48% (95% CI: 34, 60), p<0.001
Components of events contributing to Total VTE			
Proximal DVT	9 (1.1%)	19 (2.2%)	
Distal DVT	74 (9.1%)	154 (17.7%)	
Non-fatal PE	0	4 (0.5%)	
Death (any cause)	0	2 (0.2%)	
Number of Patients	**N=895**	**N=917**	
Major VTE†	9 (1.0%)	23 (2.5%)	60% (95% CI: 14, 81), p = 0.024
Number of Patients	**N=1206**	**N=1226**	
Symptomatic VTE	8 (0.7%)	24 (2.0%)	

* Relative Risk Reduction; CI = confidence interval
† Proximal DVT, nonfatal PE or VTE-related death

16 HOW SUPPLIED/STORAGE AND HANDLING

XARELTO (rivaroxaban) Tablets are available in the strengths and packages listed below:

- 10 mg tablets are round, light red, biconvex film-coated tablets marked with a triangle pointing down above a "10" on one side, and "Xa" on the other side. The tablets are supplied in the packages listed:
  - NDC 50458-580-30 Bottle containing 30 tablets
  - NDC 50458-580-10 Blister package containing 100 tablets (10 blister cards containing 10 tablets each)
- 15 mg tablets are round, red, biconvex film-coated tablets with a triangle pointing down above a "15" marked on one side and "Xa" on the other side. The tablets are supplied in the packages listed:
  - NDC 50458-578-30 Bottle containing 30 tablets
  - NDC 50458-578-90 Bottle containing 90 tablets
  - NDC 50458-578-10 Blister package containing 100 tablets (10 blister cards containing 10 tablets each)
- 20 mg tablets are triangle-shaped, dark red film-coated tablets with a triangle pointing down above a "20" marked on one side and "Xa" on the other side. The tablets are supplied in the packages listed:
  - NDC 50458-579-30 Bottle containing 30 tablets
  - NDC 50458-579-90 Bottle containing 90 tablets
  - NDC 50458-579-10 Blister package containing 100 tablets (10 blister cards containing 10 tablets each)
- Starter Pack for treatment of deep vein thrombosis and treatment of pulmonary embolism:
  - NDC 50458-584-51 30-day starter blister pack containing 51 tablets: 42 tablets of 15 mg and 9 tablets of 20 mg

Store at 25°C (77°F) or room temperature; excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Instructions for Patient Use

- Advise patients to take XARELTO only as directed.
- Remind patients to not discontinue XARELTO without first talking to their healthcare professional.
- Advise patients with atrial fibrillation to take XARELTO once daily with the evening meal.
- Advise patients with DVT and/or PE to take XARELTO 15 mg or 20 mg tablets with food at approximately the same time every day *[see Dosage and Administration (2.5)]*.
- Advise patients who cannot swallow the tablet whole to crush XARELTO and combine with a small amount of applesauce followed by food *[see Dosage and Administration (2.9)]*.
- For patients requiring an NG tube or gastric feeding tube, instruct the patient or caregiver to crush the XARELTO tablet and mix it with a small amount of water before administering via the tube *[see Dosage and Administration (2.9)]*.
- If a dose is missed, advise the patient to take XARELTO as soon as possible on the same day and continue on the following day with their recommended daily dose regimen.

Bleeding Risks

- Advise patients to report any unusual bleeding or bruising to their physician. Inform patients that it might take them longer than usual to stop bleeding, and that they may bruise and/or bleed more easily when they are treated with XARELTO *[see Warnings and Precautions (5.2)]*.
- If patients have had neuraxial anesthesia or spinal puncture, and particularly, if they are taking concomitant NSAIDs or platelet inhibitors, advise patients to watch for signs and symptoms of spinal or epidural hematoma, such as back pain, tingling, numbness (especially in the lower limbs), muscle weakness, and stool or urine incontinence. If any of these symptoms occur, advise the patient to contact his or her physician immediately *[see Boxed Warning]*.

Invasive or Surgical Procedures

Instruct patients to inform their healthcare professional that they are taking XARELTO before any invasive procedure (including dental procedures) is scheduled.

Concomitant Medication and Herbals

Advise patients to inform their physicians and dentists if they are taking, or plan to take, any prescription or over-the-counter drugs or herbals, so their healthcare professionals can evaluate potential interactions *[see Drug Interactions (7)]*.

Pregnancy and Pregnancy-Related Hemorrhage

- Advise patients to inform their physician immediately if they become pregnant or intend to become pregnant during treatment with XARELTO *[see Use in Specific Populations (8.1)]*.
- Advise pregnant women receiving XARELTO to immediately report to their physician any bleeding or symptoms of blood loss *[see Warnings and Precautions (5.7)]*.

Nursing

Advise patients to discuss with their physician if they are nursing or intend to nurse during anticoagulant treatment *[see Use in Specific Populations (8.3)]*.

Females of Reproductive Potential

Advise patients who can become pregnant to discuss pregnancy planning with their physician *[see Use in Specific Populations (8.6)]*.

XARELTO® (rivaroxaban) tablets

Active Ingredient Made in Germany

Finished Product Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

or

Bayer Pharma AG
51368 Leverkusen, Germany

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from:
Bayer HealthCare AG
51368 Leverkusen, Germany

070441-170404

MEDICATION GUIDE

XARELTO® (zah-REL-toe)
(rivaroxaban)
tablets

Read this Medication Guide before you start taking XARELTO and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about XARELTO?

- **For people taking XARELTO for atrial fibrillation**:

  People with atrial fibrillation (an irregular heart beat) are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. XARELTO lowers your chance of having a stroke by helping to prevent clots from forming. If you stop taking XARELTO, you may have increased risk of forming a clot in your blood.

  Do not stop taking XARELTO without talking to the doctor who prescribes it for you. Stopping XARELTO increases your risk of having a stroke.

  If you have to stop taking XARELTO, your doctor may prescribe another blood thinner medicine to prevent a blood clot from forming.

- **XARELTO can cause bleeding** which can be serious, and rarely may lead to death. This is because XARELTO is a blood thinner medicine that reduces blood clotting. While you take XARELTO you are likely to bruise more easily and it may take longer for bleeding to stop.

  You may have a higher risk of bleeding if you take XARELTO and take other medicines that increase your risk of bleeding, including:
  - aspirin or aspirin containing products
  - non-steroidal anti-inflammatory drugs (NSAIDs)
  - warfarin sodium (Coumadin®, Jantoven®)
  - any medicine that contains heparin
  - clopidogrel (Plavix®)
  - selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)
  - other medicines to prevent or treat blood clots

  Tell your doctor if you take any of these medicines. Ask your doctor or pharmacist if you are not sure if your medicine is one listed above.

  Call your doctor or get medical help right away if you develop any of these signs or symptoms of bleeding:
  - unexpected bleeding or bleeding that lasts a long time, such as:
    - nose bleeds that happen often
    - unusual bleeding from the gums
    - menstrual bleeding that is heavier than normal or vaginal bleeding
  - bleeding that is severe or you cannot control
  - red, pink or brown urine

XARELTO® (rivaroxaban) tablets

  - bright red or black stools (looks like tar)
  - cough up blood or blood clots
  - vomit blood or your vomit looks like "coffee grounds"
  - headaches, feeling dizzy or weak
  - pain, swelling, or new drainage at wound sites

- **Spinal or epidural blood clots (hematoma).** People who take a blood thinner medicine (anticoagulant) like XARELTO, and have medicine injected into their spinal and epidural area, or have a spinal puncture have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your risk of developing a spinal or epidural blood clot is higher if:
  - a thin tube called an epidural catheter is placed in your back to give you certain medicine
  - you take NSAIDs or a medicine to prevent blood from clotting
  - you have a history of difficult or repeated epidural or spinal punctures
  - you have a history of problems with your spine or have had surgery on your spine

  If you take XARELTO and receive spinal anesthesia or have a spinal puncture, your doctor should watch you closely for symptoms of spinal or epidural blood clots. Tell your doctor right away if you have back pain, tingling, numbness, muscle weakness (especially in your legs and feet), loss of control of the bowels or bladder (incontinence).

- **XARELTO is not for patients with artificial heart valves.**

See "What are the possible side effects of XARELTO?" for more information about side effects.

What is XARELTO?

- XARELTO is a prescription medicine used to:
  - reduce the risk of stroke and blood clots in people who have a medical condition called atrial fibrillation. With atrial fibrillation, part of the heart does not beat the way it should. This can lead to the formation of blood clots, which can travel to the brain, causing a stroke, or to other parts of the body.
  - treat blood clots in the veins of your legs (deep vein thrombosis) or lungs (pulmonary embolism) and reduce the risk of them occurring again
  - reduce the risk of forming a blood clot in the legs and lungs of people who have just had hip or knee replacement surgery

It is not known if XARELTO is safe and effective in children.

Who should not take XARELTO?

Do not take XARELTO if you:

- currently have certain types of abnormal bleeding. Talk to your doctor before taking XARELTO if you currently have unusual bleeding.
- are allergic to rivaroxaban or any of the ingredients in XARELTO. See the end of this leaflet for a complete list of ingredients in XARELTO.

What should I tell my doctor before taking XARELTO?

Before you take XARELTO, tell your doctor if you:

- have ever had bleeding problems
- have liver or kidney problems
- have any other medical condition
- are pregnant or plan to become pregnant. It is not known if XARELTO will harm your unborn baby. Tell your doctor right away if you become pregnant while taking XARELTO. If you take XARELTO during pregnancy tell your doctor right away if you have any bleeding or symptoms of blood loss.
- are breastfeeding or plan to breastfeed. It is not known if XARELTO passes into your breast milk. You and your doctor should decide if you will take XARELTO or breastfeed.

Tell all of your doctors and dentists that you are taking XARELTO. They should talk to the doctor who prescribed XARELTO for you before you have any surgery, medical or dental procedure.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Some of your other medicines may affect the way XARELTO works. Certain medicines may increase your risk of bleeding. See **"What is the most important information I should know about XARELTO?"**

Especially tell your doctor if you take:

- ketoconazole (Nizoral®)
- itraconazole (Onmel™, Sporanox®)
- ritonavir (Norvir®)
- lopinavir/ritonavir (Kaletra®)
- indinavir (Crixivan®)
- carbamazepine (Carbatrol®, Equetro®, Tegretol®, Tegretol®-XR, Teril™, Epitol®)
- phenytoin (Dilantin-125®, Dilantin®)
- phenobarbital (Solfoton™)
- rifampin (Rifater®, Rifamate®, Rimactane®, Rifadin®)
- St. John's wort (*Hypericum perforatum*)

Ask your doctor if you are not sure if your medicine is one listed above.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take XARELTO?

- Take XARELTO exactly as prescribed by your doctor.
- Do not change your dose or stop taking XARELTO unless your doctor tells you to.
- Your doctor will tell you how much XARELTO to take and when to take it.
- Your doctor may change your dose if needed.

XARELTO® (rivaroxaban) tablets

- If you take XARELTO for:
  - **atrial fibrillation:**
    - Take XARELTO 1 time a day with your evening meal.
    - If you miss a dose of XARELTO, take it as soon as you remember on the same day. Take your next dose at your regularly scheduled time.
  - **blood clots in the veins of your legs or lungs:**
    - Take XARELTO once or twice a day as prescribed by your doctor.
    - Take XARELTO with food at the same time each day.
    - If you miss a dose of XARELTO:
      - **and take XARELTO 2 times a day:** Take XARELTO as soon as you remember on the same day. You may take 2 doses at the same time to make up for the missed dose. Take your next dose at your regularly scheduled time.
      - **and take XARELTO 1 time a day:** Take XARELTO as soon as you remember on the same day. Take your next dose at your regularly scheduled time.
  - **hip or knee replacement surgery:**
    - Take XARELTO 1 time a day with or without food.
    - If you miss a dose of XARELTO, take it as soon as you remember on the same day. Take your next dose at your regularly scheduled time.
- If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take XARELTO.
- Your doctor will decide how long you should take XARELTO. Do not stop taking XARELTO without talking with your doctor first.
- Your doctor may stop XARELTO for a short time before any surgery, medical or dental procedure. Your doctor will tell you when to start taking XARELTO again after your surgery or procedure.
- Do not run out of XARELTO. Refill your prescription of XARELTO before you run out. When leaving the hospital following a hip or knee replacement, be sure that you will have XARELTO available to avoid missing any doses.
- If you take too much XARELTO, go to the nearest hospital emergency room or call your doctor right away.

What are the possible side effects of XARELTO?

- **See "What is the most important information I should know about XARELTO?"**

Tell your doctor if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XARELTO?

- Store XARELTO at room temperature between 68°F to 77°F (20° to 25°C).

Keep XARELTO and all medicines out of the reach of children.

General information about XARELTO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use XARELTO for a condition for which it was not prescribed. Do not give XARELTO to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about XARELTO. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about XARELTO that is written for health professionals.

For more information call 1-800-526-7736 or go to www.XARELTO-US.com.

What are the ingredients in XARELTO?

Active ingredient: rivaroxaban
Inactive ingredients: croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate.

The proprietary film coating mixture for XARELTO 10 mg tablets is Opadry® Pink and contains: ferric oxide red, hypromellose, polyethylene glycol 3350, and titanium dioxide.

The proprietary film coating mixture for XARELTO 15 mg tablets is Opadry® Red and contains: ferric oxide red, hypromellose, polyethylene glycol 3350, and titanium dioxide.

The proprietary film coating mixture for XARELTO 20 mg tablets is Opadry® II Dark Red and contains: ferric oxide red, polyethylene glycol 3350, polyvinyl alcohol (partially hydrolyzed), talc, and titanium dioxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Finished Product Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

or

Bayer Pharma AG
51368 Leverkusen, Germany

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from:
Bayer HealthCare AG
51368 Leverkusen, Germany

Revised: May 2016

janssen

070441-170404

APPENDIX G. PROTOCOL SUMMARY OF CHANGES (AMENDMENT 4 VS. AMENDMENT 5)

First Section of Occurrence (& throughout document)	Old Text (from Amendment 3)	New Text (Strikethrough indicates deleted text / bold italics added text)	Rationale for Revision	Substantial (S) OR Non-substantial (NS) Change
Synopsis (Efficacy Endpoints)	• Several exploratory efficacy endpoints will be evaluated. These include the following markers of pro- or anticoagulant activity: TFPI (total and free antigen, TFPI activity), PT, aPTT, ACT, FX, fibrinogen, tPA, PAP, TAFI, b-TG, PF4, and sTM.	• ***For Parts 1 and 2 of the study tissue factor pathway inhibitor (TFPI) activity, a marker of endogenous anticoagulation will be evaluated for the purpose of monitoring the potential procoagulant activity of andexanet (due to andexanet-TFPI interaction).*** • ***For Part 1 of the study the following markers will also be examined:*** PT, aPTT, ACT, FX, fibrinogen, tPA, PAP, TAFI, TFPI (total and free antigen), b-TG, PF4, and sTM.	Updated data indicate that deleted exploratory biomarker endpoints carry little clinical meaning in the context of andexanet administration.	NS
Synopsis (Safety Endpoints)	• Coagulation markers: D-dimer, F1+2, TAT, and RVVT	• Coagulation markers: D-dimer, F1+2, and TAT. ***RVVT will be collected in Part 1 only.***	Samples carry minimal clinical meaning.	NS
6.0 Enrollment and Study Procedures	A detailed description of the subject visits and clinical evaluations can be found in Appendix B: Schedule of Activities.	A detailed description of the subject visits and clinical evaluations can be found in Appendix B: Schedule of Activities (Part 1) ***and Appendix B: Schedule of Activities (Part 2).***	Added Appendix B to describe the Schedule of Activities for Part 2	NS
6.4.2. Days 2 to 4	• Collect F1+2, TAT, D-dimer, and total TFPI and TFPI activity samples within 5 minutes before FXa inhibitor administration (see Appendix B).	• Collect F1+2, TAT, D-dimer, and TFPI activity samples within 5 minutes before FXa inhibitor administration (see Appendix B, ***Appendix B). TFPI (total and free antigen) collected in Part 1 only.***	Total TFPI collected in Part 1 and not in Part 2	NS

First Section of Occurrence (& throughout document)	Old Text (from Amendment 3)	New Text (Strikethrough indicates deleted text / bold italics added text)	Rationale for Revision	Substantial (S) OR Non-substantial (NS) Change
6.9. Early Termination Visit	• Collect local laboratory samples for hematology, serum chemistry, and coagulation tests (PT, aPTT, and ACT).	• Collect local laboratory samples for hematology ***and*** serum chemistry. Coagulation tests (PT, aPTT, and ACT) ***collected in Part 1 only.***	PT, aPTT and ACT collected in Part 1 only	NS
7.1. Blood Collection	Up to approximately 815 mL of blood will be drawn from each subject over the 6 to 10 week course of the study. Approximately 650 mL of blood (comparable to the amount of blood drawn over ~10 minutes during a single Red Cross blood donation—480 mL) will be drawn over the 10 day domiciled period of the study, and the remaining amount of blood will be drawn during Screening (~31 mL) or the ~5 week post-discharge follow up period (~134 mL).	Up to approximately 815ml ***in Part 1 and 709 mL in Part 2*** of blood will be drawn from each subject over the 6 to 10 week course of the study. Approximately 650 mL ***in Part 1 and 555 mL in Part 2*** of blood (comparable to the amount of blood drawn over ~10 minutes during a single Red Cross blood donation—480 mL) will be drawn over the 10 day domiciled period of the study, and the remaining amount of blood will be drawn during Screening (~31 mL) or the ~5 week post-discharge follow up period (~134mL ***in Part 1 and ~123 mL in Part 2)***.	Removal of exploratory biomarker lab reduces the amount of blood collected in Part 2	NS
7.3.1. Coagulation Assays		***Part 2*** • ***Anti-fXa activity and thrombin generation will be measured using plasma samples collected at the site to assess the ability of observed andexanet blood levels to reverse the anticoagulant effect of apixaban, edoxaban, and rivaroxaban.*** • ***PT, aPTT, and ACT will be measured/analyzed locally at the study site at screening only.*** • ***F1+2, TAT, D-dimer (fibrin degradation fragment), and TFPI activity will be assessed in***	Clarified the coagulation assays collected in Part 2.	NS

First Section of Occurrence (& throughout document)	Old Text (from Amendment 3)	New Text (Strikethrough indicates deleted text / bold italics added text)	Rationale for Revision	Substantial (S) OR Non-substantial (NS) Change
		plasma samples collected at the site and shipped to an outside laboratory for analysis.		

First Section of Occurrence (& throughout document)	Old Text (from Amendment 3)	New Text (Strikethrough indicates deleted text / bold italics added text)	Rationale for Revision	Substantial (S) OR Non-substantial (NS) Change
10.5.1.3. Exploratory Efficacy Endpoints	Several exploratory efficacy endpoints will be evaluated. These include the following markers of pro- or anticoagulant activity: • TFPI (total and free antigen, TFPI activity) • PT • aPTT • ACT • FX • fibrinogen • tPA • PAP • TAFI • b-TG • PF4 • sTM	***For Parts 1 and 2, of the study TFPI activity, a marker of endogenous anticoagulation, will be evaluated for the purpose of monitoring the potential procoagulant activity of andexanet (due to andexanet-TFPI interactions).*** ~~Several exploratory efficacy endpoints will be evaluated. These include the following markers of pro- or anticoagulant activity:~~ • ~~TFPI (total and free antigen, TFPI activity)~~ ***For Part 1 of the study the following additional markers will also be examined:*** • PT • aPTT • ACT • FX • fibrinogen • tPA • PAP • TAFI • b-TG • PF4 • sTM • TFPI (total and free antigen)	Updated data indicate that deleted exploratory biomarker endpoints carry little clinical meaning in the context of andexanet administration.	NS
10.5.2.2. Laboratory-Based Endpoints	Immunogenicity will be evaluated by measurement of antibodies to andexanet, FX, and FXa, as well as RVVT. In addition, neutralizing antibodies for any confirmed antibody response will be measured for andexanet. Furthermore, potential neutralizing antibody activity against FX/FXa will be assessed by a clotting based modified Bethesda assay.	Immunogenicity will be evaluated by measurement of antibodies to andexanet, FX, and FXa, ~~as well as RVVT~~. In addition, neutralizing antibodies for any confirmed antibody response will be measured for andexanet. Furthermore, potential neutralizing antibody activity against FX/FXa will be assessed by a clotting based modified Bethesda assay. ***In Part 1 of the study, Russell's Viper Venon Time (RVVT) was included as an additional assessment.***	Removal of RVVT collection in Part 2.	NS

First Section of Occurrence (& throughout document)	Old Text (from Amendment 3)	New Text (Strikethrough indicates deleted text / bold italics added text)	Rationale for Revision	Substantial (S) OR Non-substantial (NS) Change
10.6.2.3. Exploratory Efficacy Analyses	Plots of the value and change from baseline over time for TFPI (total and free antigen, TFPI activity), PT, aPTT, ACT, FX, fibrinogen, tPA, PAP, TAFI, b-TG, PF4, and sTM will be evaluated by treatment in placebo-controlled cohort. If data permitted, the comparison between treatment groups may be made at an appropriate time	Plots of the value and change from baseline over time for ~~TFPI (total and free antigen~~, TFPI activity~~), PT, aPTT, ACT, FX, fibrinogen, tPA, PAP, TAFI, b-TG, PF4, and sTM~~ will be evaluated by treatment in placebo-controlled cohorts ***from all parts of the study. For Part 1 of the study, the additional exploratory endpoints of TFPI (total and free antigen), PT, aPTT, ACT, FX, fibrinogen, tPA, PAP, TAFI, b-TG, P44 and sTM were also collected and will be presented.*** If data permit~~ted~~, the comparison between treatment groups may be made at an appropriate time	Removal of TFPI (TFPI activity), PT, aPTT, ACT, FX, fibrinogen, tPA, PAP, TAFI, b-TG, PF4, and sTM in Part 2.	NS
10.6.4.4. Analysis of Laboratory Parameters	Clinical laboratory parameters including hematology, chemistry, urinalyses, and coagulation markers (D-dimer, F1+2, PT, aPTT, and ACT) will be summarized by treatment group and by time point.	Clinical laboratory parameters including hematology, chemistry, urinalyses, and coagulation markers (D-dimer, ***TAT and*** F1+2, PT, aPTT, and ACT) will be summarized by treatment group and by time point ***for the cohorts that the data was collected.***.	Clarified that TAT is included in analysis.	NS
13.0 Appendices	**APPENDIX A. STUDY EVENTS FLOW CHART** **APPENDIX B. WELLS SCORES** **APPENDIX C. US PACKAGE INSERT FOR APIXABAN (ELIQUIS)** **APPENDIX D. US PACKAGE INSERT FOR EDOXABAN (SAVAYSA)** **APPENDIX E. US PACKAGE INSERT FOR RIVAROXABAN (XARELTO)**	**APPENDIX A. STUDY EVENTS FLOW CHART (PART 1)** **APPENDIX B. STUDY EVENTS FLOW CHART (PART 2)** **APPENDIX ~~B~~C WELLS SCORES** **APPENDIX ~~C~~D US PACKAGE INSERT FOR APIXABAN (ELIQUIS)** **APPENDIX ~~D~~E US PACKAGE INSERT FOR EDOXABAN (SAVAYSA)** **APPENDIX ~~E~~ F US PACKAGE INSERT FOR RIVAROXABAN (XARELTO)**	Added Appendix B Study Events Flow Chart (Part 2).	NS

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<td>Appendix B. Study Events Flow Chart (Screening – Inpatient Day 4)</td>
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<tr><td>Local Lab: PT, aPTT, ACT</td><td>X</td><td>X</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Central Lab: F1+2, TAT, D-dimer, total TFPI, TFPI activity</td><td></td><td></td><td>X [4]</td><td>X [5]</td><td>X [5]</td><td>X [5]</td></tr>
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<tr><td>Central Lab: Fibrinogen, AT-III, FX</td><td></td><td></td><td>X [4]</td><td></td><td></td><td></td></tr>
<tr><td>Central Lab: RVVT</td><td></td><td></td><td>X [4]</td><td></td><td></td><td></td></tr>
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<tr><th>Day:</th><th>≤ -45</th><th>-1</th><th>1</th><th>2</th><th>3</th><th>4</th></tr>
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<tr><td>Local Lab: PT, aPTT, ACT</td><td>X</td><td><s>X</s></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Central Lab: F1+2, TAT, D-dimer, <s>total TFPI,</s> TFPI activity</td><td></td><td></td><td>X [4]</td><td>X [5]</td><td>X [5]</td><td>X [5]</td></tr>
<tr><td><s>Central Lab: tPA, PAP, TAFI, free TFPI, b-TG, PF4, sTM</s></td><td></td><td></td><td><s>X [4]</s></td><td></td><td></td><td></td></tr>
<tr><td><s>Central Lab: Fibrinogen, AT-III, FX</s></td><td></td><td></td><td><s>X [4]</s></td><td></td><td></td><td></td></tr>
<tr><td><s>Central Lab: RVVT</s></td><td></td><td></td><td><s>X [4]</s></td><td></td><td></td><td></td></tr>
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<td>Updated data indicate that deleted exploratory biomarker endpoints carry little clinical meaning in the context of andexanet administration.</td>
<td>NS</td>
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<tr><td>Local Lab: PT, aPTT, ACT</td><td>X</td><td></td><td colspan="7">X [3]</td><td></td></tr>
<tr><td>Central Lab: F1+2, TAT, D-dimer, Total TFPI, TFPI Activity</td><td>X</td><td></td><td colspan="7">X [3]</td><td></td></tr>
<tr><td>Central Lab: tPA, PAP, TAFI, Free TFPI, β-TG, PF4, sTM</td><td>X</td><td></td><td colspan="7">X [3]</td><td></td></tr>
<tr><td>Central Lab: Fibrinogen, AT-III, FX</td><td>X</td><td></td><td colspan="7">X [3]</td><td></td></tr>
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<tr><td>Central Lab: F1+2, TAT, D-dimer, <s>Total TFPI,</s> TFPI Activity</td><td>X</td><td></td><td colspan="7">X [3]</td><td></td></tr>
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Appendix B. Study Events Flow Chart (Day 6)	See below	See below	Updated data indicate that deleted exploratory biomarker endpoints carry little clinical meaning in the context of andexanet administration.	NS

Old Text (from Amendment 3)

Visit:	**INPT**																									
Day:	**6**																									
	Hours Post Anticoagulant Dose					**End of Bolus**		**Minutes after the Start of Andexanet Infusion**				**Hours Post Completion of Andexanet Infusion**														
Hour for Cohorts 1, 3, 5, 6:	**PRE**	**0**	**1**	**2**	**3**																					
Hour for Cohort 2:	**PRE**	**0**	**1**	**2**	**4**																					
Hour for Cohorts 4, 7:	**PRE**	**0**	**1**		**1.5**	**End Bolus (+2 min)**	**End Bolus (+5 min)**	**45 min**	**90 min**	**110 min**	**End Infu-sion (-2 min)**	**5 min**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4.5**	**5.5**	**6.5**	**7.5**	**8.5**	**14.5**
Hours for Cohorts 8-10:	**PRE**	**0**	**1**	**2**	**8**																					
~~Local Lab: PT, aPTT, ACT~~	~~X~~				~~X~~	~~X~~		~~X~~				~~X~~	~~X~~		~~X~~		~~X~~		~~X~~			~~X~~		~~X~~	
Central Lab: F1+2, TAT, D-dimer, ~~Total TFPI,~~ TFPI activity	X				X	X	X	X		X		X	X		X		X					X			X
~~Central Lab: tPA, PAP, TAFI, Free TFPI, β-TG, PF4, sTM~~	~~X~~				~~X~~	~~X~~	~~X~~	~~X~~		~~X~~		~~X~~	~~X~~		~~X~~		~~X~~					~~X~~			~~X~~
~~Fibrinogen, AT-III, FX~~	~~X~~				~~X~~	~~X~~	~~X~~	~~X~~		~~X~~		~~X~~	~~X~~													

<table>
<tr><th>First Section of Occurrence (& throughout document)</th><th>Old Text (from Amendment 3)</th><th>New Text (Strikethrough indicates deleted text / bold italics added text)</th><th>Rationale for Revision</th><th>Substantial (S) OR Non-substantial (NS) Change</th></tr>
<tr>
<td>Appendix B. Study Events Flow Chart (Day 7-10)</td>
<td>
<table>
<tr><th>Visit:</th><th colspan="4">INPT</th><th>INPT</th><th>Discharge</th></tr>
<tr><th>Day:</th><th colspan="4">7</th><th>8</th><th>9</th><th>10</th></tr>
<tr><th></th><th colspan="4">Hours Post Last Anticoagulant Dose</th><th></th><th></th></tr>
<tr><th></th><th>24</th><th>36</th><th>48</th><th>60</th><th>0</th><th>0</th></tr>
<tr><td>Local Lab: PT, aPTT, ACT</td><td>X</td><td></td><td>X</td><td></td><td>X</td><td>X</td></tr>
<tr><td>Central Lab: F1+2, TAT, D-dimer, Total TFPI, TFPI activity</td><td>X</td><td></td><td>X</td><td></td><td>X</td><td>X</td></tr>
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<td>NS</td>
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36)	Central Lab: F1+2, TAT, D-dimer, Total TFPI, TFPI Activity	X	X	Central Lab: F1+2, TAT, D-dimer, ~~Total TFPI,~~ TFPI Activity	X	X	endpoints carry little clinical meaning in the context of andexanet administration.	
	Central Lab: tPA, PAP, TAFI, Free TFPI, b-TG, PF4, sTM	X	X	~~Central Lab: tPA, PAP, TAFI, Free TFPI, b-TG, PF4, sTM~~	~~X~~	~~X~~		
	Central Lab: Fibrinogen, AT-III, FX	X	X	~~Central Lab: Fibrinogen, AT-III, FX~~	~~X~~	~~X~~		
	Central Lab: RVVT	X	X	~~Central Lab: RVVT~~	~~X~~	~~X~~		