CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202439Orig1s035

Trade Name:	Xarelto
Generic or Proper Name:	(rivaroxaban) tablets
Sponsor:	Jannsen Pharmaceuticals, Inc.
Approval Date:	August 23, 2021
Indication:	Xarelto, in combination with aspirin, is indicated to reduce the risk of major thrombotic vascular events (myocardial infarction, ischemic stroke, acute limb ischemia, and major amputation of a vascular etiology) in patients with PAD, including patients who have recently undergone a lower extremity revascularization procedure due to symptomatic PAD.

CENTER FOR DRUG EVALUATION AND RESEARCH

202439Orig1s035

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202439Orig1s035

APPROVAL LETTER

NDA 202439/S-035
NDA 022406/S-037

SUPPLEMENT APPROVAL

Jannsen Pharmaceuticals, Inc.
Attention: Huy Truong
Director, Global Regulatory Affairs
920 US Highway 202, PO Box 300
Raritan, NJ 08869-0602

Dear Mr. Truong:

Please refer to your supplemental new drug application (sNDA) for NDA 202439 dated October 23, 2020, received October 23, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xarelto (rivaroxaban) tablets.

We also refer to your supplemental new drug application (sNDA) for NDA 022406 dated June 4, 2021, received June 4, 2021, submitted under Section 505(b) for Xarelto (rivaroxaban) tablets to maintain harmonization of Xarelto labeling.

These Prior Approval supplemental new drug applications provide for the following indication:

Xarelto, in combination with aspirin, is indicated to reduce the risk of major thrombotic vascular events (myocardial infarction, ischemic stroke, acute limb ischemia, and major amputation of a vascular etiology) in patients with PAD, including patients who have recently undergone a lower extremity revascularization procedure due to symptomatic PAD.

Xarelto had an indication in patients with Coronary Artery Disease or Peripheral Artery Disease; these uses are now separately described. This supplement and the VOYAGER-PAD study add initiation of Xarelto in patients with a recent revascularization procedure.

Changes were also made to Sections 1 INDICATIONS AND USAGE, 2 DOSING AND ADMINISTRATION, 6 ADVERSE REACTIONS, 8 USE IN SPECIFIC POPULATIONS and 14 CLINICAL STUDIES of the Package Insert. Minor editorial changes were made throughout. The Medication Guide was also updated to include information for this new indication.

APPROVAL & LABELING

We have completed our review of these applications, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application (202439/S-035) because necessary studies are impossible or highly impracticable because peripheral artery disease due to atherosclerosis does not occur in children.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Bridget Kane, Regulatory Project Manager, at (240) 402-2170.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NORMAN L STOCKBRIDGE
08/23/2021 04:45:45 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202439Orig1s035

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XARELTO® 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. (2.2, 2.3, 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----------

Indications and Usage (1.7, 1.8)	08/2021
Dosage and Administration (2.1)	08/2021

----------INDICATIONS AND USAGE----------

XARELTO is a factor Xa inhibitor indicated:

- to reduce risk of stroke and systemic embolism in nonvalvular atrial fibrillation (1.1)
- for treatment of deep vein thrombosis (DVT) (1.2)
- for treatment of pulmonary embolism (PE) (1.3)
- for reduction in the risk of recurrence of DVT or PE (1.4)
- for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery (1.5)
- for prophylaxis of venous thromboembolism (VTE) in acutely ill medical patients (1.6)
- to reduce the risk of major cardiovascular events in patients with coronary artery disease (CAD) (1.7)
- to reduce the risk of major thrombotic vascular events in patients with peripheral artery disease (PAD), including patients after recent lower extremity revascularization due to symptomatic PAD (1.8)

----------DOSAGE AND ADMINISTRATION----------

- Nonvalvular Atrial Fibrillation: 15 or 20 mg, once daily with food (2.1)
- Treatment of DVT and/or PE: 15 mg orally twice daily with food for the first 21 days followed by 20 mg orally once daily with food for the remaining treatment (2.1)
- Reduction in the Risk of Recurrence of DVT and/or PE in patients at continued risk for DVT and/or PE: 10 mg once daily with or without food, after at least 6 months of standard anticoagulant treatment (2.1)
- Prophylaxis of DVT Following Hip or Knee Replacement Surgery: 10 mg orally once daily with or without food (2.1)
- Prophylaxis of VTE in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding: 10 mg once daily, with or without food, in hospital and after hospital discharge for a total recommended duration of 31 to 39 days (2.1)
- CAD or PAD: 2.5 mg orally twice daily with or without food, in combination with aspirin (75-100 mg) once daily (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 2.5 mg, 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. An agent to reverse the activity of rivaroxaban is available. (5.2)
- Pregnancy-related hemorrhage: Use XARELTO with caution in pregnant women due to the potential for obstetric hemorrhage and/or emergent delivery. (5.7, 8.1)
- Prosthetic heart valves: XARELTO use not recommended (5.8)
- Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome: XARELTO use not recommended. (5.10)

----------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----------

- Avoid combined P-gp and strong CYP3A inhibitors and inducers (7 2, 7.3)
- Anticoagulants: Avoid concomitant use (7.4)

----------USE IN SPECIFIC POPULATIONS----------

- Renal impairment: Avoid or adjust dose (8.6)
- Hepatic impairment: Avoid use in Child-Pugh B and C hepatic impairment or hepatic disease associated with coagulopathy (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*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 (2.2, 2.3), 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/or Pulmonary Embolism

XARELTO is indicated for the reduction in the risk of recurrence of DVT and/or PE in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months.

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.

1.6 Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding

XARELTO is indicated for the prophylaxis of venous thromboembolism (VTE) and VTE related death during hospitalization and post hospital discharge in adult patients admitted for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE and not at high risk of bleeding *[see Warnings and Precautions (5.2) and Clinical Studies (14.5)]*.

1.7 Reduction of Risk of Major Cardiovascular Events in Patients with Coronary Artery Disease (CAD)

XARELTO, in combination with aspirin, is indicated to reduce the risk of major cardiovascular events (cardiovascular death, myocardial infarction, and stroke) in patients with coronary artery disease.

1.8 Reduction of Risk of Major Thrombotic Vascular Events in Patients with Peripheral Artery Disease (PAD), Including Patients after Lower Extremity Revascularization due to Symptomatic PAD

XARELTO, in combination with aspirin, is indicated to reduce the risk of major thrombotic vascular events (myocardial infarction, ischemic stroke, acute limb ischemia, and major amputation of a vascular etiology) in patients with PAD, including patients who have recently undergone a lower extremity revascularization procedure due to symptomatic PAD.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Table 1: Recommended Dosage

Indication	Renal Considerations*	Dosage	Food/Timing†
Reduction in Risk of Stroke in Nonvalvular Atrial Fibrillation	CrCl >50 mL/min	20 mg once daily	Take with evening meal
	CrCl ≤50 mL/min‡	15 mg once daily	Take with evening meal
Treatment of DVT and/or PE	CrCl ≥15 mL/min‡	15 mg twice daily **▼ after 21 days, transition to ▼** 20 mg once daily	Take with food, at the same time each day
	CrCl <15 mL/min	Avoid Use	
Reduction in the Risk of Recurrence of DVT and/or PE in patients at continued risk for DVT and/or PE	CrCl ≥15 mL/min‡	10 mg once daily, after at least 6 months of standard anticoagulant treatment	Take with or without food
	CrCl <15 mL/min	Avoid Use	
Prophylaxis of DVT Following:			
- **Hip Replacement Surgery**§	CrCl ≥15 mL/min‡	10 mg once daily for 35 days, 6-10 hours after surgery once hemostasis has been established	Take with or without food
	CrCl <15 mL/min	Avoid Use	
- **Knee Replacement Surgery**§	CrCl ≥15 mL/min‡	10 mg once daily for 12 days, 6-10 hours after surgery once hemostasis has been established	Take with or without food
	CrCl <15 mL/min	Avoid Use	
Prophylaxis of VTE in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding	CrCl ≥15 mL/min‡	10 mg once daily, in hospital and after hospital discharge, for a total recommended duration of 31 to 39 days	Take with or without food
	CrCl <15 mL/min	Avoid Use	
Reduction of Risk of Major Cardiovascular Events (CV Death, MI, and Stroke) in CAD	No dose adjustment needed based on CrCl	2.5 mg twice daily, plus aspirin (75-100 mg) once daily	Take with or without food
Reduction of Risk of Major Thrombotic Vascular Events in PAD, Including Patients after Lower Extremity Revascularization due to Symptomatic PAD	No dose adjustment needed based on CrCl	2.5 mg twice daily, plus aspirin (75-100 mg) once daily. When starting therapy after a successful lower extremity revascularization procedure, initiate once hemostasis has been established.	Take with or without food

* *Calculate CrCl based on actual weight. [See Warnings and Precautions (5.4) and Use in Specific Populations (8.6)]*

† *See Clinical Pharmacology (12.3)*

‡ *Patients with CrCl <30 mL/min were not studied, but administration of XARELTO is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment (CrCl 30 to <50 mL/min) [see Use in Specific Populations (8.6)]*

§ *See Dosage and Administration (2.3)*

2.2 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.

2.3 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.

2.4 Missed Dose

- For patients receiving 2.5 mg twice daily: if a dose is missed, the patient should take a single 2.5 mg XARELTO dose as recommended at the next scheduled time.
- For patients receiving 15 mg twice daily: The patient should take XARELTO immediately to ensure intake of 30 mg XARELTO per day. Two 15 mg tablets may be taken at once.

- For patients receiving 20 mg, 15 mg or 10 mg once daily: The patient should take the missed XARELTO dose immediately. The dose should not be doubled within the same day to make up for a missed dose.

2.5 Administration Options

For patients who are unable to swallow whole tablets, XARELTO tablets (all strengths) 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. Administration with food is not required for the 2.5 mg or 10 mg tablets *[see Clinical Pharmacology (12.3)]*.

Administration via nasogastric (NG) tube or gastric feeding tube: After confirming gastric placement of the tube, XARELTO tablets (all strengths) 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. Enteral feeding is not required following administration of the 2.5 mg or 10 mg tablets *[see Clinical Pharmacology (12.3)]*.

Crushed XARELTO tablets (all strengths) 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.

3 DOSAGE FORMS AND STRENGTHS

- 2.5 mg tablets: Round, light yellow, and film-coated with a triangle pointing down above a “2.5” marked on one side and “Xa” on the other side
- 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 (2.2, 2.3) 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, dual antiplatelet therapy, 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 CYP3A inhibitors increases rivaroxaban exposure and may increase bleeding risk *[see Drug Interactions (7.2)]*.

Risk of Hemorrhage in Acutely Ill Medical Patients at High Risk of Bleeding

Acutely ill medical patients with the following conditions are at increased risk of bleeding with the use of XARELTO for primary VTE prophylaxis: history of bronchiectasis, pulmonary cavitation, or pulmonary hemorrhage, active cancer (i.e. undergoing acute, in-hospital cancer treatment), active gastroduodenal ulcer in the three months prior to treatment, history of bleeding in the three months prior to treatment, or dual antiplatelet therapy. XARELTO is not for use for primary VTE prophylaxis in these hospitalized, acutely ill medical patients at high risk of bleeding.

Reversal of Anticoagulant Effect

An agent to reverse the anti-factor Xa activity of rivaroxaban is available. Because of high plasma protein binding, rivaroxaban is not dialyzable *[see Clinical Pharmacology (12.3)]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. 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 efficacy and safety studies. Monitoring for the anticoagulation effect of rivaroxaban using a clotting test (PT, INR or aPTT) or anti-factor Xa (FXa) activity is not recommended.

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 XARELTO and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of XARELTO *[see Clinical Pharmacology (12.3)]*. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of XARELTO 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 (2.1)]*. Consider dose adjustment or discontinuation of XARELTO in patients who develop acute renal failure while on XARELTO *[see Use in Specific Populations (8.6)]*.

Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE

In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO in these patients.

Discontinue XARELTO in patients who develop acute renal failure while on treatment *[see Use in Specific Populations (8.6)]*.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO in these patients.

Discontinue XARELTO in patients who develop acute renal failure while on treatment *[see Use in Specific Populations (8.6)]*.

Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding

In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO in these patients.

Discontinue XARELTO in patients who develop acute renal failure while on treatment *[see Use in Specific Populations (8.6)]*.

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 (8.7)]*.

5.6 Use with P-gp and Strong CYP3A Inhibitors or Inducers

Avoid concomitant use of XARELTO with known combined P-gp and strong CYP3A inhibitors *[see Drug Interactions (7.2)]*.

Avoid concomitant use of XARELTO with drugs that are known combined P-gp and strong CYP3A 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. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress) *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1)]*.

5.8 Patients with Prosthetic Heart Valves

On the basis of the GALILEO study, use of XARELTO is not recommended in patients who have had transcatheter aortic valve replacement (TAVR) because patients randomized to XARELTO experienced higher rates of death and bleeding compared to those randomized to an anti-platelet regimen. The safety and efficacy of XARELTO have not been studied in patients with other prosthetic heart valves or other valve procedures. Use of XARELTO is not recommended in patients with prosthetic heart valves.

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.

5.10 Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome

Direct-acting oral anticoagulants (DOACs), including XARELTO, are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

6 ADVERSE REACTIONS

The following clinically significant 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, 34,947 patients were exposed to XARELTO.

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 2 shows the number of patients experiencing various types of bleeding events in the ROCKET AF trial.

Table 2: 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.

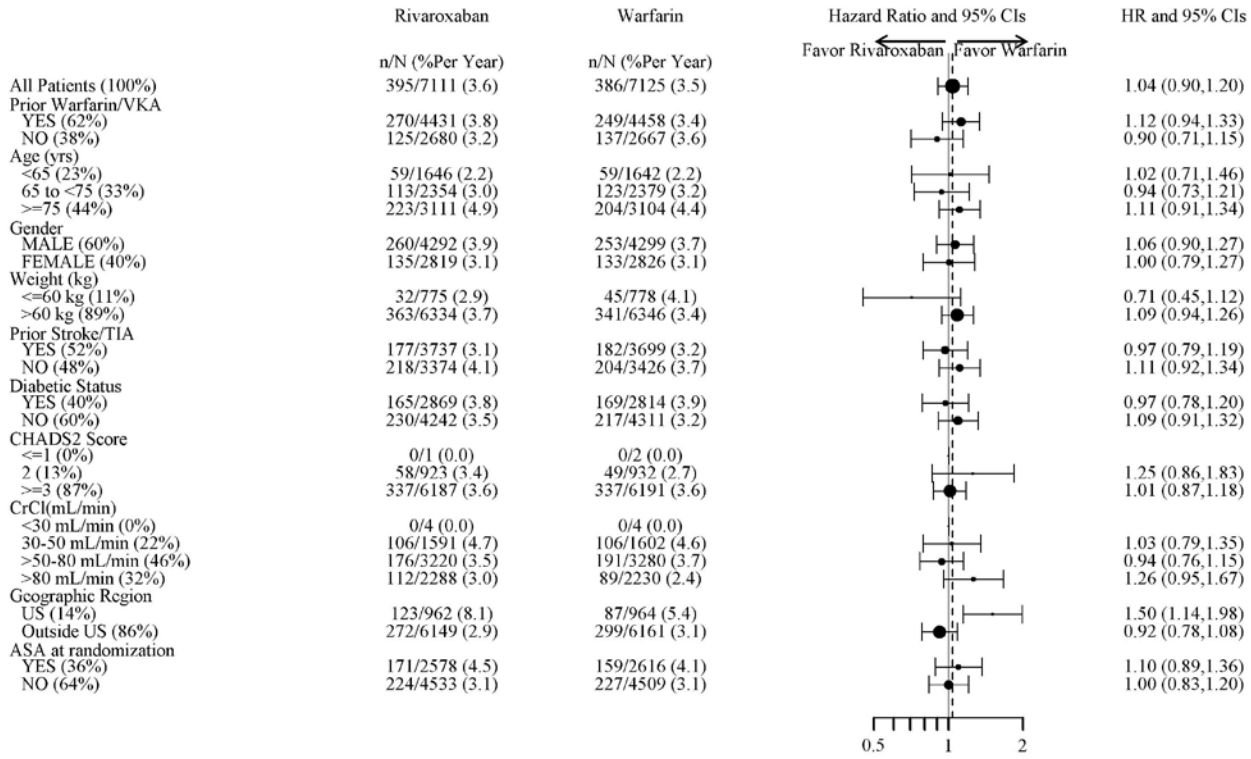
§ Hemorrhagic stroke in this table specifically refers to non-traumatic intraparenchymal and/or intraventricular hematoma in patients on treatment plus 2 days.

¶ 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) and/or Pulmonary Embolism (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 3 shows the number of patients experiencing major bleeding events in the pooled analysis of the EINSTEIN DVT and EINSTEIN PE studies.

Table 3: 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

§ 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

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

EINSTEIN CHOICE Study

In the EINSTEIN CHOICE clinical study, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 1% for XARELTO 10 mg, 2% for XARELTO 20 mg, and 1% for acetylsalicylic acid (aspirin) 100 mg. The mean duration of treatment was 293 days for XARELTO 10 mg-treated patients and 286 days for aspirin 100 mg-treated patients.

Table 4 shows the number of patients experiencing bleeding events in the EINSTEIN CHOICE study.

Table 4: Bleeding Events* in EINSTEIN CHOICE

Parameter	XARELTO† 10 mg N=1127 n (%)	Acetylsalicylic Acid (aspirin)† 100 mg N=1131 n (%)
Major bleeding event	5 (0.4)	3 (0.3)
Fatal bleeding	0	1 (<0.1)
Non-fatal critical organ bleeding	2 (0.2)	1 (<0.1)
Non-fatal non-critical organ bleeding‡	3 (0.3)	1 (<0.1)
Clinically relevant non-major (CRNM) bleeding§	22 (2.0)	20 (1.8)
Any bleeding	151 (13.4)	138 (12.2)

* 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 10 mg once daily or aspirin 100 mg once daily.

‡ 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.

§ Bleeding which was clinically overt, did not meet the criteria for major bleeding, but was associated with medical intervention, unscheduled contact with a physician, temporary cessation of treatment, discomfort for the patient, or impairment of activities of daily life.

In the EINSTEIN CHOICE study, there was an increased incidence of bleeding, including major and CRNM bleeding in the XARELTO 20 mg group compared to the XARELTO 10 mg or aspirin 100 mg groups.

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 5.

Table 5: 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.

Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding

In the MAGELLAN study, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events. Cases of pulmonary hemorrhage and pulmonary

hemorrhage with bronchiectasis were observed. Patients with bronchiectasis/pulmonary cavitation, active cancer (i.e., undergoing acute, in-hospital cancer treatment), dual antiplatelet therapy or active gastroduodenal ulcer or any bleeding in the previous three months all had an excess of bleeding with XARELTO compared with enoxaparin/placebo and are excluded from all MAGELLAN data presented in Table 6. The incidence of bleeding leading to drug discontinuation was 2.5% for XARELTO vs. 1.4% for enoxaparin/placebo.

Table 6 shows the number of patients experiencing various types of bleeding events in the MAGELLAN study.

Table 6: Bleeding Events in MAGELLAN[*] Study–Safety Analysis Set - On Treatment Plus 2 Days

MAGELLAN Study[¶]	XARELTO 10 mg N=3218 n (%)	Enoxaparin 40 mg /placebo N=3229 n (%)
Major bleeding[‡†]	22 (0.7)	15 (0.5)
Critical site bleeding	7 (0.2)	4 (0.1)
Fatal bleeding[§]	3 (<0.1)	1 (<0.1)
Clinically relevant non-major bleeding events (CRNM)	93 (2.9)	34 (1.1)

* Patients at high risk of bleeding (i.e. bronchiectasis/pulmonary cavitation, active cancer, dual antiplatelet therapy or active gastroduodenal ulcer or any bleeding in the previous three months) were excluded.

† 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 drop 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.

§ Fatal bleeding is adjudicated death with the primary cause of death from bleeding.

¶ Patients received either XARELTO or placebo once daily for 35 ±4 days starting in hospital and continuing post hospital discharge or received enoxaparin or placebo once daily for 10 ±4 days in the hospital.

Reduction of Risk of Major Cardiovascular Events in Patients with CAD

In the COMPASS trial overall, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 2.7% for XARELTO 2.5 mg twice daily vs. 1.2% for placebo on background therapy for all patients with aspirin 100 mg once daily. The incidences of important bleeding events in the CAD and PAD populations in COMPASS were similar.

Table 7 shows the number of patients experiencing various types of major bleeding events in the COMPASS trial.

Table 7: Major Bleeding Events in COMPASS - On Treatment Plus 2 days*

Parameter	XARELTO† N=9134 n (%/year)	Placebo† N=9107 n (%/year)	XARELTO vs. Placebo HR (95 % CI)
Modified ISTH Major Bleeding‡	263 (1.6)	144 (0.9)	1.8 (1.5, 2.3)
- Fatal bleeding event	12 (<0.1)	8 (<0.1)	1.5 (0.6, 3.7)
Intracranial hemorrhage (ICH)	6 (<0.1)	3 (<0.1)	2.0 (0.5, 8.0)
Non-intracranial	6 (<0.1)	5 (<0.1)	1.2 (0.4, 4.0)
- Symptomatic bleeding in critical organ (non-fatal)	58 (0.3)	43 (0.3)	1.4 (0.9, 2.0)
- ICH (fatal and non-fatal)	23 (0.1)	21 (0.1)	1.1 (0.6, 2.0)
Hemorrhagic Stroke	18 (0.1)	13 (<0.1)	1.4 (0.7, 2.8)
Other ICH	6 (<0.1)	9 (<0.1)	0.7 (0.2, 1.9)
- Bleeding into the surgical site requiring reoperation (non-fatal, not in critical organ)	7 (<0.1)	6 (<0.1)	1.2 (0.4, 3.5)
- Bleeding leading to hospitalization (non-fatal, not in critical organ, not requiring reoperation)	188 (1.1)	91 (0.5)	2.1 (1.6, 2.7)
Major GI bleeding	117 (0.7)	49 (0.3)	2.4 (1.7, 3.4)

* 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 in the safety analysis set in COMPASS patients.

† Treatment schedule: XARELTO 2.5 mg twice daily or placebo. All patients received background therapy with aspirin 100 mg once daily.

‡ Defined as i) fatal bleeding, or ii) symptomatic bleeding in a critical area or organ, such as intraarticular, intramuscular with compartment syndrome, intraspinal, intracranial, intraocular, respiratory, pericardial, liver, pancreas, retroperitoneal, adrenal gland or kidney; or iii) bleeding into the surgical site requiring reoperation, or iv) bleeding leading to hospitalization.

CI: confidence interval; HR: hazard ratio; ISTH: International Society on Thrombosis and Hemostasis

Reduction of Risk of Major Thrombotic Vascular Events in Patients with Peripheral Artery Disease (PAD), Including Patients after Lower Extremity Revascularization due to Symptomatic PAD

The incidence of premature permanent discontinuation due to bleeding events for XARELTO 2.5 mg twice daily vs. placebo on background therapy with aspirin 100 mg once daily in VOYAGER was 4.1% vs. 1.6% and in COMPASS PAD was 2.7% vs. 1.3%, respectively.

Table 8 shows the number of patients experiencing various types of TIMI (Thrombolysis in Myocardial Infarction) major bleeding events in the VOYAGER trial. The most common site of bleeding was gastrointestinal.

Table 8: Major Bleeding Events* in VOYAGER- On Treatment Plus 2 days

	XARELTO† N=3256		Placebo† N=3248		XARELTO vs. Placebo HR (95 % CI)
Parameter	**n (%)**	**Event rate %/year**	**n (%)**	**Event rate %/year**	
TIMI Major Bleeding (CABG/non-CABG)	62 (1.9)	0.96	44 (1.4)	0.67	1.4 (1.0, 2.1)
Fatal bleeding	6 (0.2)	0.09	6 (0.2)	0.09	1.0 (0.3, 3.2)
Intracranial bleeding	13 (0.4)	0.20	17 (0.5)	0.26	0.8 (0.4, 1.6)
Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or drop in hematocrit of ≥15%	46 (1.4)	0.71	24 (0.7)	0.36	1.9 (1.2, 3.2)

* Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories.

† Treatment schedule: XARELTO 2.5 mg twice daily or placebo. All patients received background therapy with aspirin 100 mg once daily.

CABG: Coronary artery bypass graft; CI: confidence interval; HR: hazard ratio; TIMI: Thrombolysis in Myocardial Infarction Bleeding Criteria

Other Adverse Reactions

Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in the EINSTEIN DVT and EINSTEIN PE studies are shown in Table 9.

Table 9: Other Adverse Reactions* Reported by ≥1% of XARELTO-Treated Patients in EINSTEIN DVT and EINSTEIN PE Studies

Body System Adverse Reaction		
EINSTEIN DVT Study	**XARELTO 20 mg N=1718 n (%)**	**Enoxaparin/VKA N=1711 n (%)**
Gastrointestinal disorders		
Abdominal pain	46 (2.7)	25 (1.5)
General disorders and administration site conditions		
Fatigue	24 (1.4)	15 (0.9)
Musculoskeletal and connective tissue disorders		
Back pain	50 (2.9)	31 (1.8)
Muscle spasm	23 (1.3)	13 (0.8)
Nervous system disorders		
Dizziness	38 (2.2)	22 (1.3)
Psychiatric disorders		
Anxiety	24 (1.4)	11 (0.6)
Depression	20 (1.2)	10 (0.6)
Insomnia	28 (1.6)	18 (1.1)
EINSTEIN PE Study	**XARELTO 20 mg N=2412 n (%)**	**Enoxaparin/VKA N=2405 n (%)**
Skin and subcutaneous tissue disorders		
Pruritus	53 (2.2)	27 (1.1)

* Adverse reaction with Relative Risk >1.5 for XARELTO versus comparator

Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in RECORD 1-3 studies are shown in Table 10.

Table 10: Other Adverse Drug Reactions* Reported by ≥1% of XARELTO-Treated Patients in RECORD 1-3 Studies

Body System 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)

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of XARELTO. 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

Hepatobiliary disorders: jaundice, cholestasis, hepatitis (including hepatocellular injury)

Immune system disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, angioedema

Nervous system disorders: hemiparesis

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS)

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 CYP3A inhibitors increase exposure to rivaroxaban and may increase the risk of bleeding. Combined P-gp and strong CYP3A inducers decrease exposure to rivaroxaban and may increase the risk of thromboembolic events.

7.2 Drugs that Inhibit Cytochrome P450 3A Enzymes and Drug Transport Systems

Interaction with Combined P-gp and Strong CYP3A Inhibitors

Avoid concomitant administration of XARELTO with known combined P-gp and strong CYP3A 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 CYP3A 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 CYP3A 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 CYP3A 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 3A Enzymes and Drug Transport Systems

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A 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

Risk Summary

The limited available data on XARELTO in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Use XARELTO with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery. The anticoagulant effect of XARELTO cannot be reliably monitored with standard laboratory testing. Consider the benefits and risks of XARELTO for the mother and possible risks to the fetus when prescribing XARELTO to a pregnant woman *[see Warnings and Precautions (5.2, 5.7)]*.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Pregnancy is a risk factor for venous thromboembolism and that risk is increased in women with inherited or acquired thrombophilias. Pregnant women with thromboembolic disease have an increased risk of maternal complications including pre-eclampsia. Maternal thromboembolic disease increases the risk for intrauterine growth restriction, placental abruption and early and late pregnancy loss.

Fetal/Neonatal Adverse Reactions

Based on the pharmacologic activity of Factor Xa inhibitors and the potential to cross the placenta, bleeding may occur at any site in the fetus and/or neonate.

Labor or Delivery

All patients receiving anticoagulants, including pregnant women, are at risk for bleeding and this risk may be increased during labor or delivery *[see Warnings and Precautions (5.7)]*. The risk of bleeding should be balanced with the risk of thrombotic events when considering the use of XARELTO in this setting.

Data

Human Data

There are no adequate or well-controlled studies of XARELTO in pregnant women, and dosing for pregnant women has not been established. Post-marketing experience is currently insufficient

to determine a rivaroxaban-associated risk for major birth defects or miscarriage. In an *in vitro* placenta perfusion model, unbound rivaroxaban was rapidly transferred across the human placenta.

Animal Data

Rivaroxaban crosses the placenta in animals. 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 during the period of organogenesis. This dose corresponds to about 14 times the human exposure of unbound drug. In rats, peripartal 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).

8.2 Lactation

Risk Summary

Rivaroxaban has been detected in human milk. There are insufficient data to determine the effects of rivaroxaban on the breastfed child or on milk production. Rivaroxaban and/or its metabolites were present in the milk of rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XARELTO and any potential adverse effects on the breastfed infant from XARELTO or from the underlying maternal condition *(see Data)*.

Data

Animal Data

Following a single oral administration of 3 mg/kg of radioactive [^{14}C]-rivaroxaban to lactating rats between Day 8 to 10 postpartum, the concentration of total radioactivity was determined in milk samples collected up to 32 hours post-dose. The estimated amount of radioactivity excreted with milk within 32 hours after administration was 2.1% of the maternal dose.

8.3 Females and Males of Reproductive Potential

Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants including XARELTO should be assessed in females of reproductive potential and those with abnormal uterine bleeding.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of adult patients in clinical trials for the approved indications of XARELTO (N=64,943 patients), 64 percent were 65 years and over, with 27 percent 75 years and over. 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 *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

8.6 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

Patients with Chronic Kidney Disease not on Dialysis

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 <30 mL/min were not studied, but administration of XARELTO 15 mg once daily is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment *[see 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/or PE

In the EINSTEIN trials, patients with CrCl values <30 mL/min at screening were excluded from the studies, but administration of XARELTO is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment (CrCl 30 to <50 mL/min) *[see Clinical Pharmacology (12.3)]*. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 15 to <30 mL/min. Avoid the use of XARELTO in patients with CrCl <15 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. In the RECORD 1-3 trials, patients with CrCl values <30 mL/min at screening were excluded from the studies, but administration of XARELTO 10 mg once daily is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment (CrCl 30 to <50 mL/min) *[see Clinical Pharmacology (12.3)]*. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 15 to <30 mL/min. Avoid the use of XARELTO in patients with CrCl <15 mL/min.

Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding

Patients with CrCl values <30 mL/min at screening were excluded from the MAGELLAN study. In patients with CrCl <30 mL/min a dose of XARELTO 10 mg once daily is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment (CrCl 30 to <50 mL/min) *[see Clinical Pharmacology (12.3)]*. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 15 to <30 mL/min. Avoid use of XARELTO in patients with CrCl <15 mL/min.

Reduction of Risk of Major Cardiovascular Events in Patients with CAD and Reduction of Risk of Major Thrombotic Vascular Events in Patients with PAD, Including Patients After Recent Lower Extremity Revascularization due to Symptomatic PAD

Patients with Chronic Kidney Disease not on Dialysis

Patients with a CrCl <15 mL/min at screening were excluded from COMPASS and VOYAGER, and limited data are available for patients with a CrCl of 15 to 30 mL/min. In patients with CrCl <30 mL/min, a dose of 2.5 mg XARELTO twice daily is expected to give an exposure similar to that in patients with moderate renal impairment (CrCl 30 to <50 mL/min) *[see Clinical Pharmacology (12.3)]*, whose efficacy and safety outcomes were similar to those with preserved renal function.

Patients with End-Stage Renal Disease on Dialysis

No clinical outcome data is available for the use of XARELTO with aspirin in patients with ESRD on dialysis since these patients were not enrolled in COMPASS or VOYAGER. In patients with ESRD maintained on intermittent hemodialysis, administration of XARELTO 2.5 mg twice daily will result in concentrations of rivaroxaban and pharmacodynamic activity similar to those observed in moderate renal impaired patients in the COMPASS study *[see Clinical Pharmacology (12.2, 12.3)]*. It is not known whether these concentrations will lead to similar CV risk reduction and bleeding risk in patients with ESRD on dialysis as was seen in COMPASS.

8.7 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)]*.

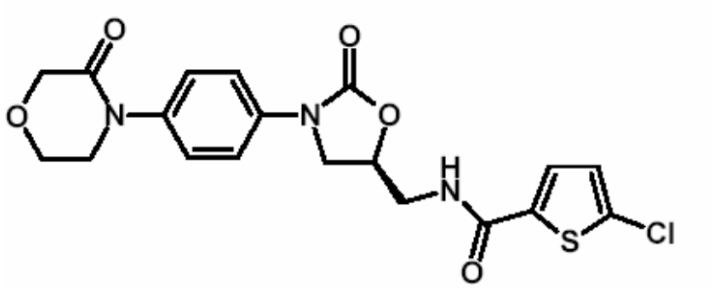
Avoid the use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy.

10 OVERDOSAGE

Overdose of XARELTO may lead to hemorrhage. Discontinue XARELTO and initiate appropriate therapy if bleeding complications associated with overdosage occur. 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. An agent to reverse the anti-factor Xa activity of rivaroxaban is available.

11 DESCRIPTION

Rivaroxaban, a factor Xa (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 2.5 mg, 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 2.5 mg is Opadry® Light Yellow, containing ferric oxide yellow, hypromellose, polyethylene glycol 3350, and titanium dioxide, and 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 (8.6)]*.

Table 11: 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 2.5 mg and 10 mg dose, it is estimated to be 80% to 100% and is not affected by food. XARELTO 2.5 mg and 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 (2.1)]*.

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

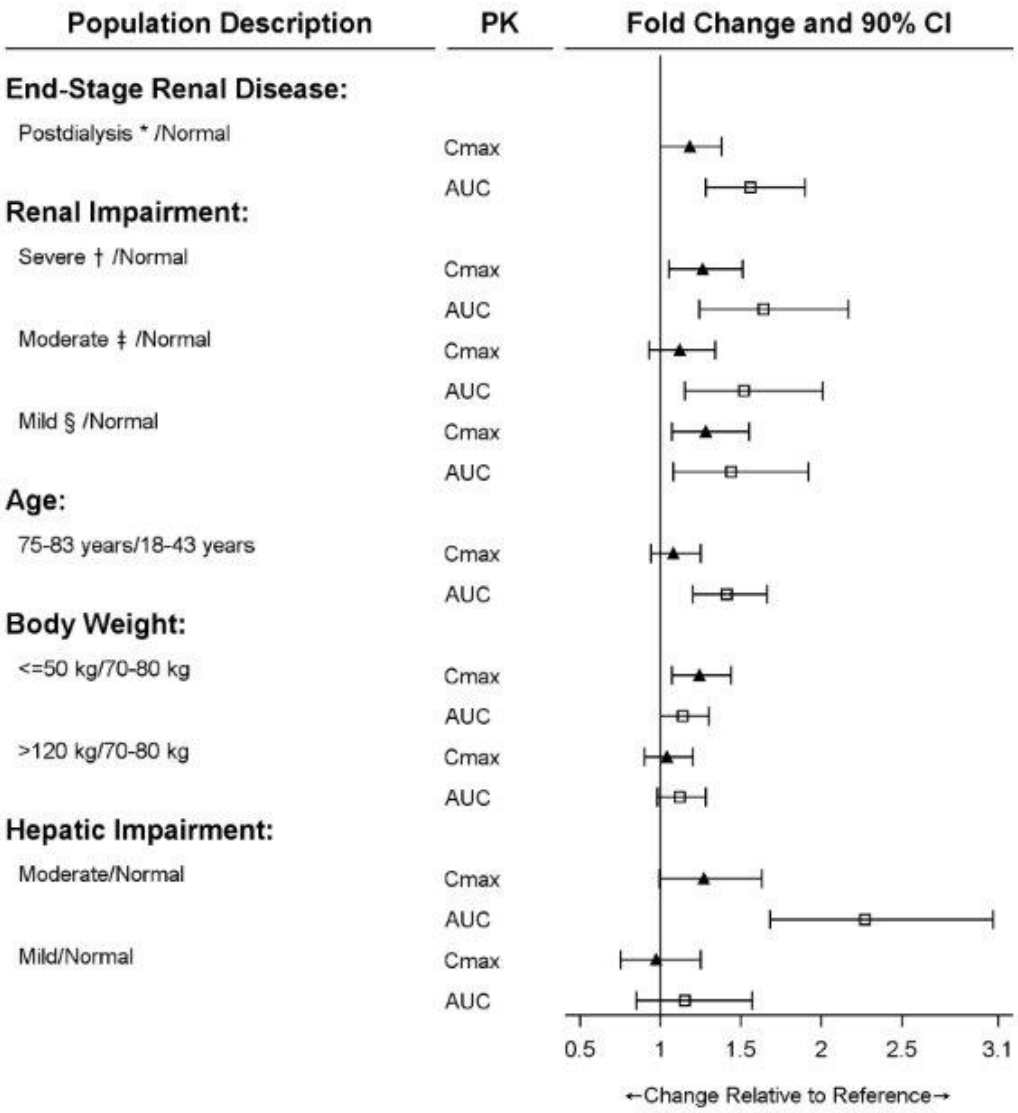
In a Phase 1 study, following the administration of [^{14}C]-rivaroxaban, approximately one-third (36%) was recovered as unchanged drug in the urine and 7% was recovered as unchanged drug in feces. Unchanged drug is excreted into urine, mainly via active tubular secretion and to a lesser extent via glomerular 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.

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.
‡ Creatinine clearance 30 to 49 mL/min.
§ Creatinine clearance 50 to 79 mL/min.

[See Dosage and Administration (2.1)]

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 (8.6)]*.

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 11). 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

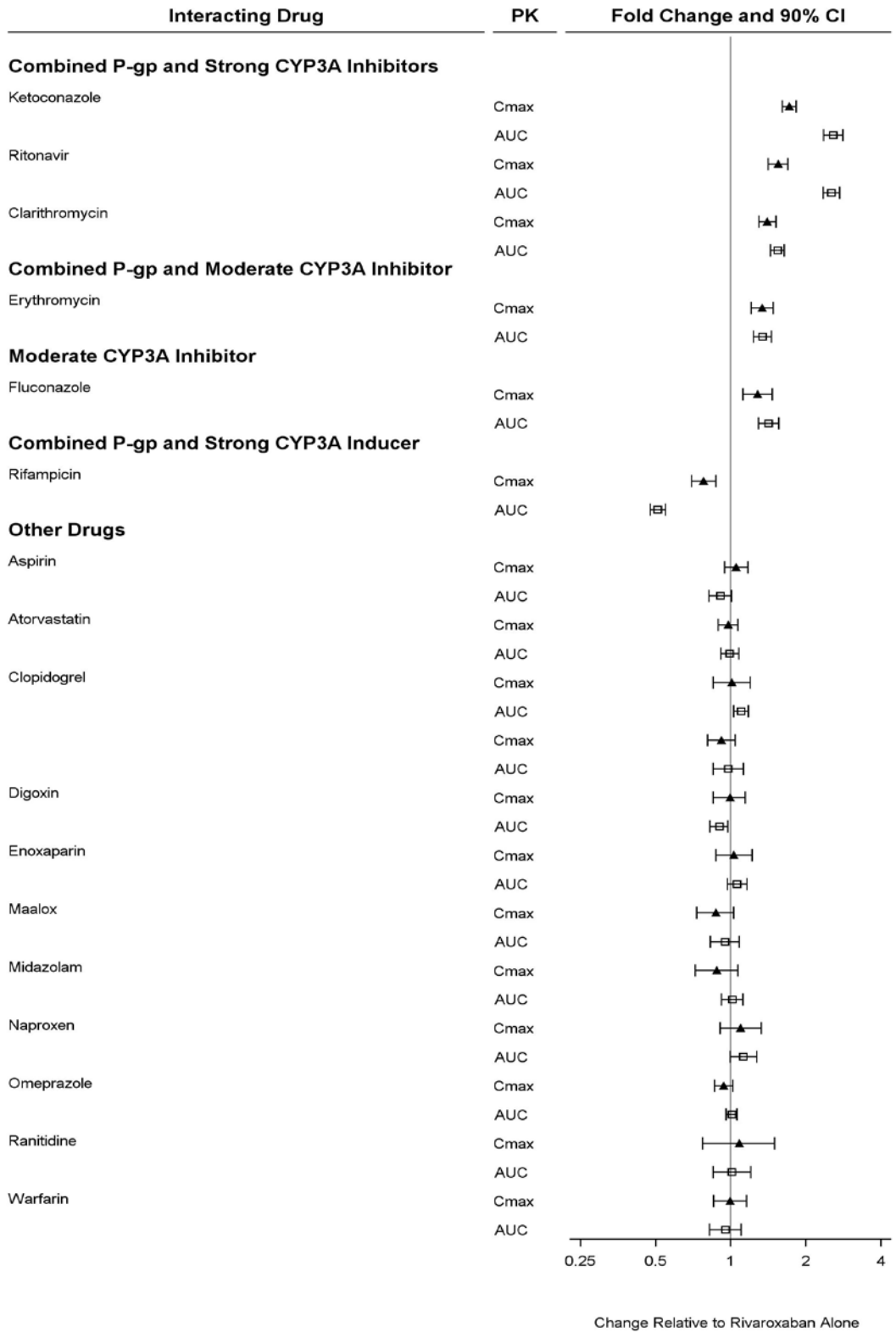
The safety and pharmacokinetics of single-dose XARELTO (10 mg) were evaluated in a study in healthy subjects (n=16) and subjects with varying degrees of hepatic impairment (see Figure 2). No patients with severe hepatic impairment (Child-Pugh C) were studied. Compared to healthy subjects with normal 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 (8.7)]*.

Drug Interactions

In vitro studies indicate that rivaroxaban neither inhibits the major cytochrome P450 enzymes CYP1A2, 2C8, 2C9, 2C19, 2D6, 2J2, and 3A nor induces CYP1A2, 2B6, 2C19, or 3A. *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)]*.

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 3A 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 CYP3A 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 Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonist for the prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) [NCT00403767], 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:
  - age ≥75 years,
  - hypertension,
  - heart failure or left ventricular ejection fraction ≤35%, or
  - 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 12 displays the overall results for the primary composite endpoint and its components.

Table 12: Primary Composite Endpoint Results in ROCKET AF Study (Intent-to-Treat Population)

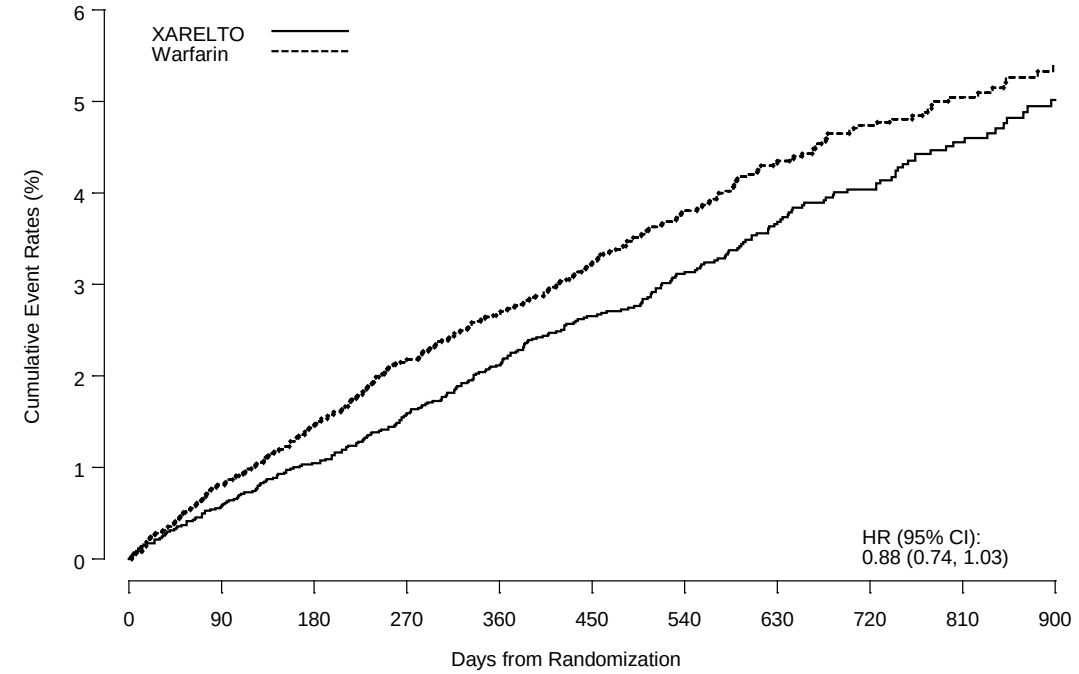
	XARELTO		Warfarin		XARELTO vs. Warfarin
Event	**N=7081 n (%)**	**Event Rate (per 100 Pt-yrs)**	**N=7090 n (%)**	**Event Rate (per 100 Pt-yrs)**	**Hazard Ratio (95% CI)**
Primary Composite Endpoint*	269 (3.8)	2.1	306 (4.3)	2.4	0.88 (0.74, 1.03)
Stroke	253 (3.6)	2.0	281 (4.0)	2.2	
Hemorrhagic Stroke†	33 (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)

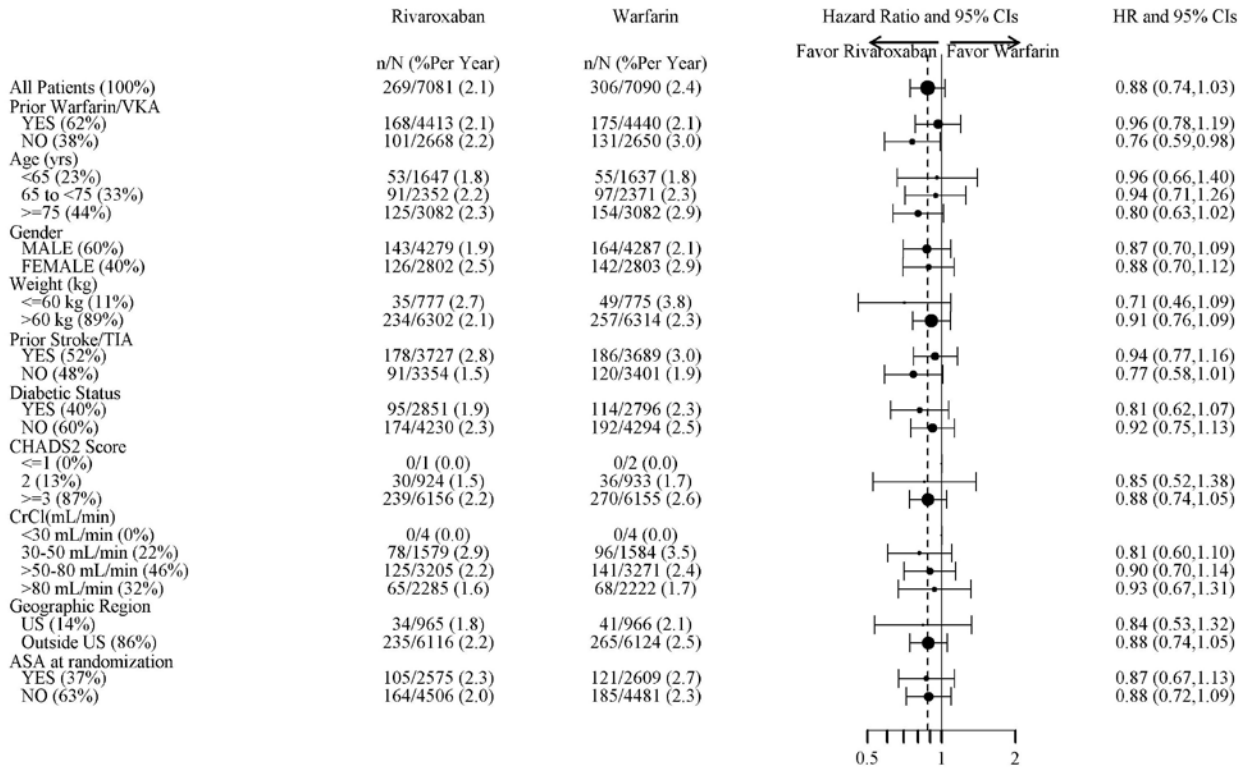


Number of Subjects at Risk:

XARELTO	7081	6927	6774	6620	6470	5580	4779	3820	2951	2058	1321
Warfarin	7090	6910	6755	6590	6440	5561	4756	3807	2944	2069	1319

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.
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) and/or Pulmonary Embolism (PE)

EINSTEIN Deep Vein Thrombosis and EINSTEIN Pulmonary Embolism Studies

XARELTO for the treatment of DVT and/or PE was studied in EINSTEIN DVT [NCT00440193] and EINSTEIN PE [NCT00439777], 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 13 displays the overall results for the primary composite endpoint and its components for EINSTEIN DVT and EINSTEIN PE studies.

Table 13: Primary Composite Endpoint Results* in EINSTEIN DVT and EINSTEIN PE Studies – Intent-to-Treat Population

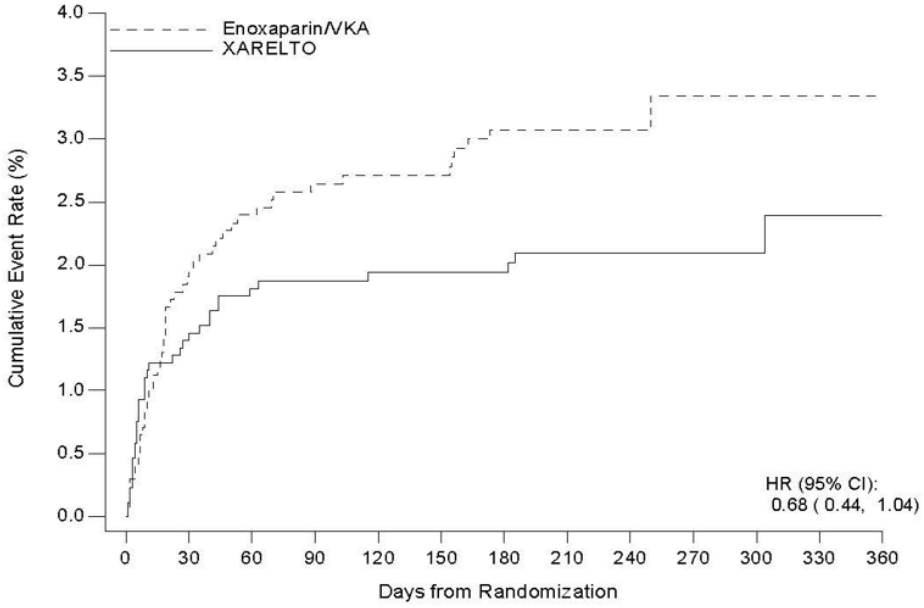
Event	XARELTO 20 mg†	Enoxaparin/VKA†	XARELTO vs. Enoxaparin/VKA Hazard Ratio (95% CI)
EINSTEIN DVT Study	**N=1731 n (%)**	**N=1718 n (%)**	
Primary Composite Endpoint	36 (2.1)	51 (3.0)	0.68 (0.44, 1.04)
Death (PE)	1 (<0.1)	0	
Death (PE cannot be excluded)	3 (0.2)	6 (0.3)	
Symptomatic PE and DVT	1 (<0.1)	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.

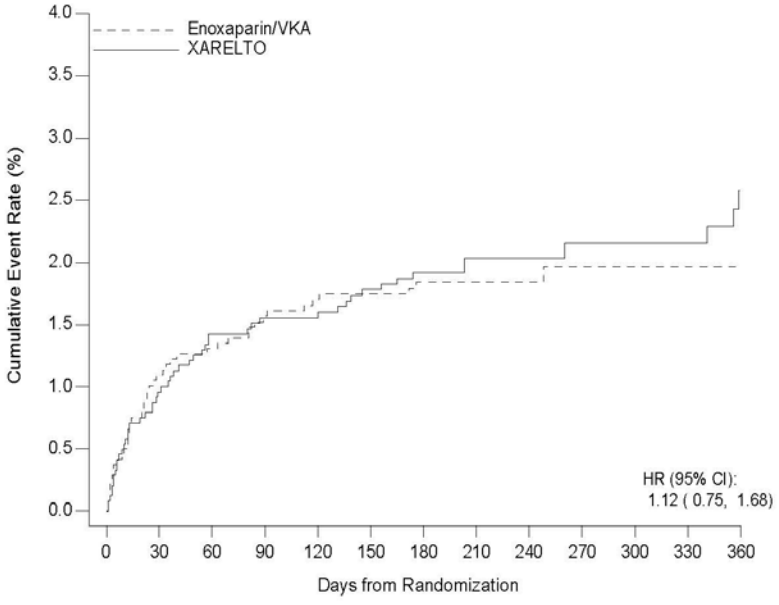
Figure 6: Time to First Occurrence of the Composite of Recurrent DVT or Non-fatal or Fatal PE by Treatment Group (Intent-to-Treat Population) – EINSTEIN DVT Study



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

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

14.3 Reduction in the Risk of Recurrence of DVT and/or PE

EINSTEIN CHOICE Study

XARELTO for reduction in the risk of recurrence of DVT and of PE was evaluated in the EINSTEIN CHOICE study [NCT02064439], a multi-national, double-blind, superiority study comparing XARELTO (10 or 20 mg once daily with food) to 100 mg acetylsalicylic acid (aspirin) once daily in patients who had completed 6 to 12 months of anticoagulant treatment for DVT and/or PE following the acute event. The intended treatment duration in the study was up to 12 months. Patients with an indication for continued therapeutic-dose anticoagulation were excluded.

Because the benefit-risk assessment favored the 10 mg dose versus aspirin compared to the 20 mg dose versus aspirin, only the data concerning the 10 mg dose is discussed below.

A total of 2275 patients were randomized and followed on study treatment for a mean of 290 days for the XARELTO and aspirin treatment groups. The mean age was approximately 59 years. The population was 56% male, 70% Caucasian, 14% Asian and 3% Black. In the EINSTEIN CHOICE study, 51% of patients had DVT only, 33% had PE only, and 16% had PE and DVT combined. Other risk factors included idiopathic VTE (43%), previous episode of DVT/PE (17%), recent surgery or trauma (12%), prolonged immobilization (10%), use of estrogen containing drugs (5%), known thrombophilic conditions (6%), Factor V Leiden gene mutation (4%), or active cancer (3%).

In the EINSTEIN CHOICE study, XARELTO 10 mg was demonstrated to be superior to aspirin 100 mg for the primary composite endpoint of time to first occurrence of recurrent DVT or non-fatal or fatal PE.

Table 14 displays the overall results for the primary composite endpoint and its components.

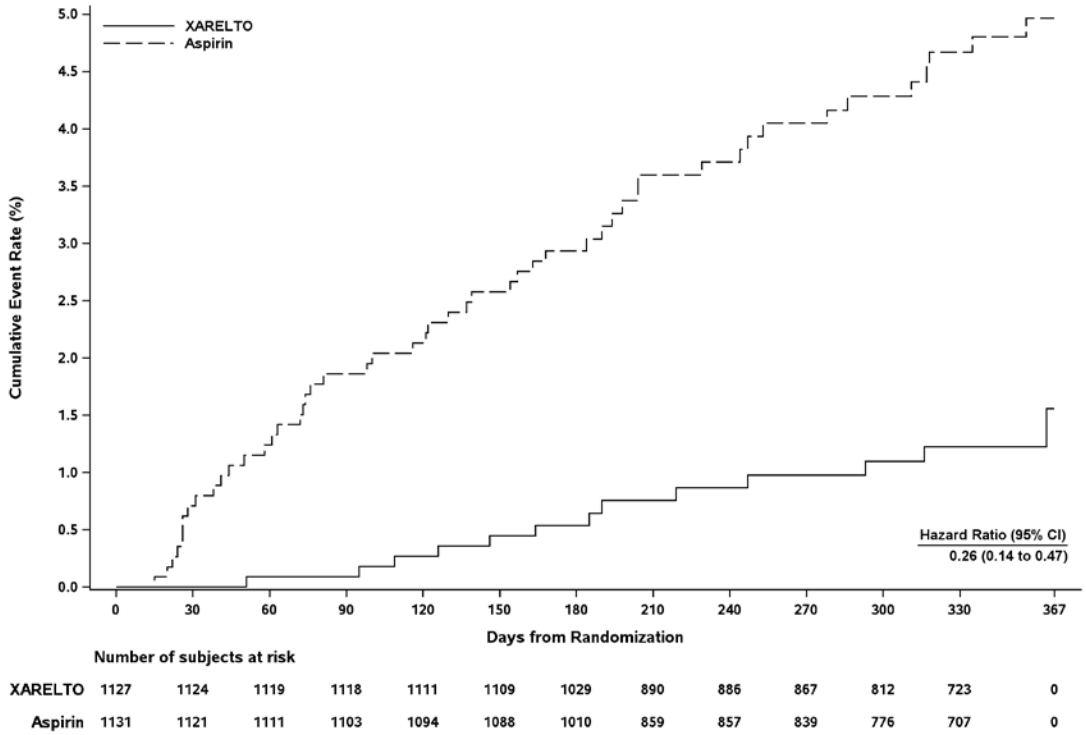
Table 14: Primary Composite Endpoint and its Components Results* in EINSTEIN CHOICE Study – Full Analysis Set

Event	XARELTO 10 mg N=1,127 n (%)	Acetylsalicylic Acid (Aspirin) 100 mg N=1,131 n (%)	XARELTO 10 mg vs. Aspirin 100 mg Hazard Ratio (95% CI)
Primary Composite Endpoint	13 (1.2)	50 (4.4)	0.26 (0.14, 0.47) p<0.0001
Symptomatic recurrent DVT	8 (0.7)	29 (2.6)	
Symptomatic recurrent PE	5 (0.4)	19 (1.7)	
Death (PE)	0	1 (<0.1)	
Death (PE cannot be excluded)	0	1 (<0.1)	

* For the primary efficacy analysis, all confirmed events were considered from randomization up to the end of intended treatment duration (12 months) irrespective of the actual treatment duration. The individual component of the primary endpoint represents the first occurrence of the event.

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 (Full Analysis Set) – EINSTEIN CHOICE Study



14.4 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 REgulation of Coagulation in ORthopedic Surgery to Prevent DVT and PE, Controlled, Double-blind, Randomized Study of BAY 59-7939 in the Extended Prevention of VTE in Patients Undergoing Elective Total Hip or Knee Replacement (RECORD 1, 2, and 3) [NCT00329628, NCT00332020, NCT00361894] 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 15.

Table 15: 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%)	

* 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 16.

Table 16: 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

14.5 Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding

The efficacy and safety of XARELTO for prophylaxis of venous thromboembolism in acutely ill medical patients at risk for thromboembolic complications not at high risk of bleeding was evaluated in the MAGELLAN study (Multicenter, rAndomized, parallel Group Efficacy and safety study for the prevention of venous thromboembolism in hospitalized medically iLL patients comparing rivaroxabaN with enoxaparin [NCT00571649]). MAGELLAN was a multicenter, randomized, double-blind, parallel-group efficacy and safety study comparing XARELTO to enoxaparin, in the prevention of VTE in hospitalized acutely ill medical patients during the in-hospital and post-hospital discharge period. Eligible patients included adults who were at least 40 years of age, hospitalized for an acute medical illness, at risk of VTE due to moderate or severe immobility, and had additional risk factors for VTE. The population at risk of VTE was required to have one or more of the following VTE risk factors, i.e. prolonged immobilization, age ≥75 years, history of cancer, history of VTE, history of heart failure, thrombophilia, acute infectious disease contributing to the hospitalization and BMI ≥35 kg/m^2). The causes for hospitalization included heart failure, active cancer, acute ischemic stroke, acute infectious and inflammatory disease and acute respiratory insufficiency. Patients were randomized to receive either XARELTO 10 mg once daily for 35 ±4 days starting in hospital and continuing post hospital discharge (n=4050) or enoxaparin 40 mg once daily for 10 ±4 days starting in hospital followed by placebo post-discharge (n=4051).

The major efficacy outcome in the MAGELLAN trial was a composite endpoint that included asymptomatic proximal deep venous thrombosis (DVT) in lower extremity, symptomatic proximal

or distal DVT in the lower extremity, symptomatic non-fatal pulmonary embolism (PE), and death related to venous thromboembolism (VTE).

A total of 6024 patients were evaluable for the major efficacy outcome analysis (2967 on XARELTO 10 mg once daily and 3057 on enoxaparin/placebo). The mean age was 68.9 years, with 37.1% of the subject population ≥ 75 years. VTE risk factors included severe immobilization at study entry (99.9%), D-dimer > 2X ULN (43.7%), history of heart failure (35.6%), BMI ≥ 35 kg/m^2 (15.2%), chronic venous insufficiency (14.9%), acute infectious disease (13.9%), severe varicosis (12.5%), history of cancer (16.2%), history of VTE (4.5%), hormone replacement therapy (1.1%), and thrombophilia (0.3%), recent major surgery (0.8%) and recent serious trauma (0.2%). The population was 54.7% male, 68.2% White, 20.4% Asian, 1.9% Black and 5.3% Other. Admitting diagnoses for hospitalization were acute infectious diseases (43.8%) followed by congestive heart failure NYHA class III or IV (33.2%), acute respiratory insufficiency (26.4%), acute ischemic stroke (18.5%) and acute inflammatory diseases (3.4%).

Table 17 shows the overall results from the prespecified, modified intent-to-treat (mITT) analysis for the efficacy outcomes and their components. This analysis excludes approximately 25% of the patients mainly due to no ultrasonographic assessment (13.5%), inadequate assessment at day 35 (8.1%), or lack of intake of study medication (1.3%).

Table 17: Efficacy Results at Day 35 (modified Intent-to-Treat) and at Day 10 (per protocol) in the MAGELLAN Study

Events from Day 1 to Day 35, mITT analysis set	**XARELTO 10 mg N=2967 n (%)**	**Enoxaparin 40 mg/ placebo N=3057 n (%)**	**RR (95% CI)**
Primary Composite Endpoint at Day 35	131 (4.4%)	175 (5.7%)	0.77 (0.62, 0.96)
Symptomatic non-fatal PE	10 (0.3)	14 (0.5)	
Symptomatic DVT in lower extremity	13 (0.4)	15 (0.5)	
Asymptomatic proximal DVT in lower extremity	103 (3.5)	133 (4.4)	
VTE related death	19 (0.6)	30 (1.0)	
Events from Day 1 to Day 10, PP analysis set	**XARELTO 10 mg N=2938 n (%)**	**Enoxaparin 40 mg N=2993 n (%)**	**RR (95% CI)**
Primary Composite Endpoint at Day 10	78 (2.7)	82 (2.7)	0.97 (0.71, 1.31)
Symptomatic non-fatal PE	6 (0.2)	2 (<0.1)	
Symptomatic DVT in lower extremity	7 (0.2)	6 (0.2)	
Asymptomatic proximal DVT in lower extremity	71 (2.4)	71 (2.4)	
VTE related death	3 (0.1)	6 (0.2)	
mITT analysis set plus all-cause mortality	**N=3096 n (%)**	**N=3169 n (%)**	**RR (95% CI)**
Other Composite Endpoint at Day 35	266 (8.6)	293 (9.2)	0.93 (0.80, 1.09)
Symptomatic non-fatal PE	10 (0.3)	14 (0.4)	
Symptomatic DVT in lower extremity	13 (0.4)	15 (0.5)	
Asymptomatic proximal DVT in lower extremity	103 (3.3)	133 (4.2)	
All-cause mortality	159 (5.1)	153 (4.8)	

mITT: modified intent-to-treat; PP: per protocol; DVT: Deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism; CI: Confidence Interval; RR: Relative Risk

Patients with bronchiectasis/pulmonary cavitation, active cancer, dual antiplatelet therapy or active gastroduodenal ulcer or any bleeding in the previous three months (19.4%) all had an excess of bleeding with XARELTO compared with enoxaparin/placebo. Therefore, patients meeting these criteria were excluded from the following analyses presented below.

Table 18 provides the efficacy results for the subgroup of patients not at a high risk of bleeding.

Table 18: Efficacy Results at Day 35 (modified Intent-to-Treat) and at Day 10 (per protocol) in patients not at a high risk of bleeding in the MAGELLAN Study*

Events from Day 1 to Day 35, mITT analysis set	**XARELTO 10 mg N=2419 n (%)**	**Enoxaparin 40 mg/ placebo N=2506 n (%)**	**RR (95% CI)**
Primary Composite Endpoint at Day 35	94 (3.9)	143 (5.7)	0.68 (0.53, 0.88)
Symptomatic non-fatal PE	7 (0.3)	10 (0.4)	
Symptomatic DVT in lower extremity	9 (0.4)	10 (0.4)	
Asymptomatic proximal DVT in lower extremity	73 (3.0)	110 (4.4)	
VTE related death	15 (0.6)	26 (1.0)	
Events from Day 1 to Day 10, PP analysis set	**XARELTO 10 mg N=2385 n (%)**	**Enoxaparin 40 mg N=2433 n (%)**	**RR (95% CI)**
Primary Composite Endpoint at Day 10	58 (2.4)	72 (3.0)	0.82 (0.58, 1.15)
Symptomatic non-fatal PE	5 (0.2)	2 (<0.1)	
Symptomatic DVT in lower extremity	6 (0.3)	4 (0.2)	
Asymptomatic proximal DVT in lower extremity	52 (2.2)	62 (2.5)	
VTE related death	2 (<0.1)	6 (0.2)	
mITT analysis set plus all-cause mortality	**N=2504 n (%)**	**N=2583 n (%)**	**RR (95% CI)**
Other Composite Endpoint at Day 35	184 (7.3)	225 (8.7)	0.84 (0.70, 1.02)
Symptomatic non-fatal PE	7 (0.3)	10 (0.4)	
Symptomatic DVT in lower extremity	9 (0.4)	10 (0.4)	
Asymptomatic proximal DVT in lower extremity	73 (2.9)	110 (4.3)	
All-cause mortality	107 (4.3)	112 (4.3)	

* Patients at high risk of bleeding (i.e. bronchiectasis/pulmonary cavitation, active cancer, dual antiplatelet therapy or active gastroduodenal ulcer or any bleeding in the previous three months) were excluded.

mITT: modified intent-to-treat; PP: per protocol; DVT: Deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism; CI: Confidence Interval; RR: Relative Risk

14.6 Reduction of Risk of Major Cardiovascular Events in Patients with CAD

The evidence for the efficacy and safety of XARELTO for the reduction in the risk of stroke, myocardial infarction, or cardiovascular death in patients with coronary artery disease (CAD) or peripheral artery disease (PAD) was derived from the double-blind, placebo-controlled Cardiovascular OutcoMes for People using Anticoagulation StrategieS trial (COMPASS) [NCT10776424]. A total of 27,395 patients were evenly randomized to rivaroxaban 2.5 mg orally twice daily plus aspirin 100 mg once daily, rivaroxaban 5 mg orally twice daily alone, or aspirin 100 mg once daily alone. Because the 5 mg dose alone was not superior to aspirin alone, only the data concerning the 2.5 mg dose plus aspirin are discussed below.

Patients with established CAD or PAD were eligible. Patients with CAD who were younger than 65 years of age were also required to have documentation of atherosclerosis involving at least two vascular beds or to have at least two additional cardiovascular risk factors (current smoking, diabetes mellitus, an estimated glomerular filtration rate [eGFR] <60 mL per minute, heart failure, or non-lacunar ischemic stroke ≥1 month earlier). Patients with PAD were either symptomatic with ankle brachial index <0.90 or had asymptomatic carotid artery stenosis ≥50%, a previous carotid revascularization procedure, or established ischemic disease of one or both lower extremities. Patients were excluded for use of dual antiplatelet, other non-aspirin antiplatelet, or oral anticoagulant therapies, ischemic, non-lacunar stroke within 1 month, hemorrhagic or lacunar stroke at any time, or eGFR <15 mL/min.

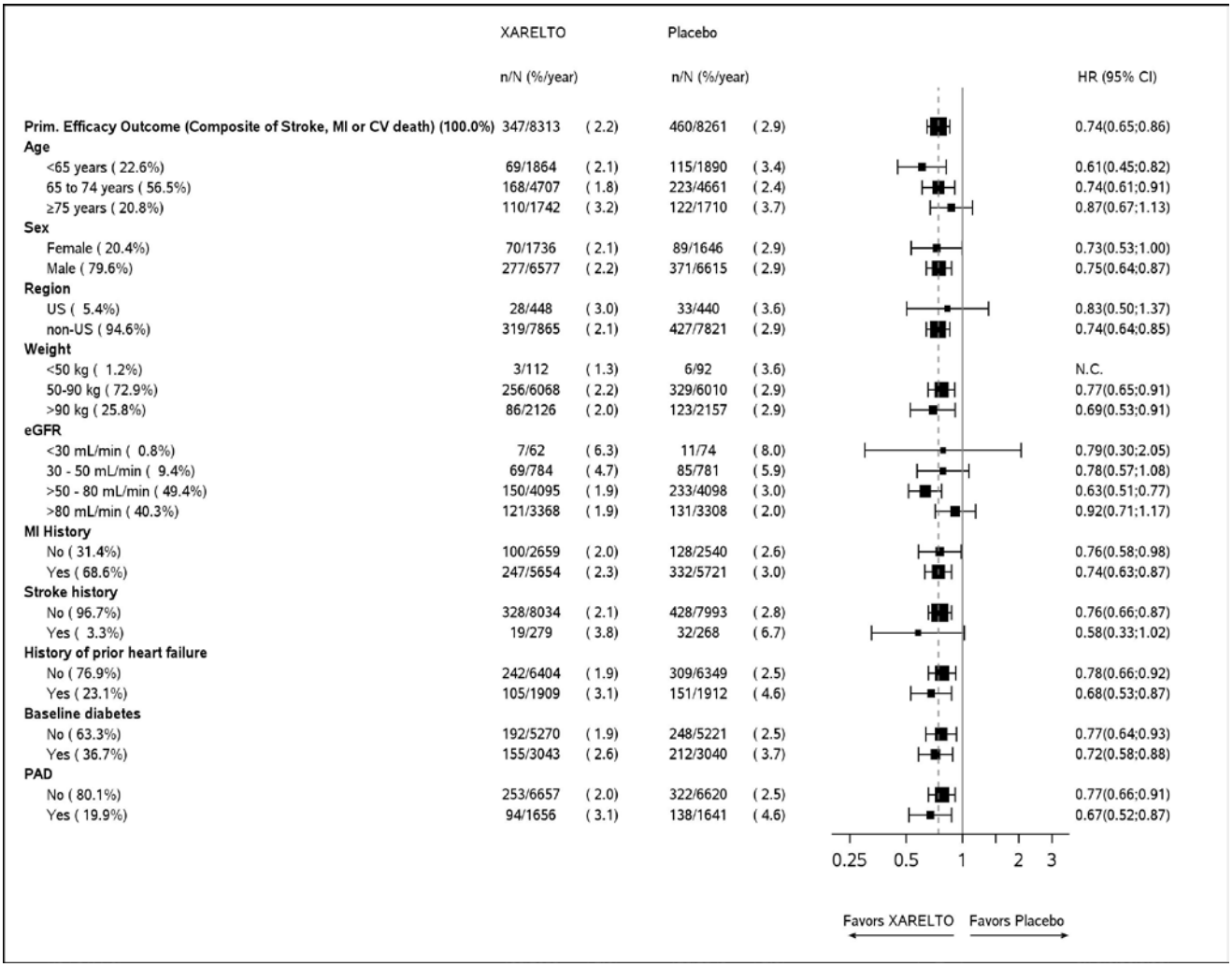
The mean age was 68 years and 21% of the subject population were ≥75 years. Of the included patients, 91% had CAD (and will be referred to as the COMPASS CAD population), 27% had PAD (and will be referred to as the COMPASS PAD population), and 18% had both CAD and PAD. Of the patients with CAD, 69% had prior MI, 60% had prior percutaneous transluminal coronary angioplasty (PTCA)/atherectomy/ percutaneous coronary intervention (PCI), and 26% had history of coronary artery bypass grafting (CABG) prior to study. Of the patients with PAD, 49% had intermittent claudication, 27% had peripheral artery bypass surgery or peripheral percutaneous transluminal angioplasty, 26% had asymptomatic carotid artery stenosis > 50%, and 4% had limb or foot amputation for arterial vascular disease.

The mean duration of follow-up was 23 months. Relative to placebo, XARELTO reduced the rate of the primary composite outcome of stroke, myocardial infarction or cardiovascular death: HR 0.76 (95% CI: 0.66, 0.86; p=0.00004). In the COMPASS CAD population, the benefit was observed early with a constant treatment effect over the entire treatment period (see Table 19 and Figure 10).

A benefit-risk analysis of the data from COMPASS was performed by comparing the number of CV events (CV deaths, myocardial infarctions and non-hemorrhagic strokes) prevented to the number of fatal or life-threatening bleeding events (fatal bleeds + symptomatic non-fatal bleeds into a critical organ) in the XARELTO group versus the placebo group. Compared to placebo, during 10,000 patient-years of treatment, XARELTO would be expected to result in 70 fewer CV events and 12 additional life-threatening bleeds, indicating a favorable balance of benefits and risks.

The results in the COMPASS CAD population were consistent across major subgroups (see Figure 9).

Figure 9: Risk of Primary Efficacy Outcome by Baseline Characteristics in the COMPASS CAD Population (Intent-to-Treat Population)*



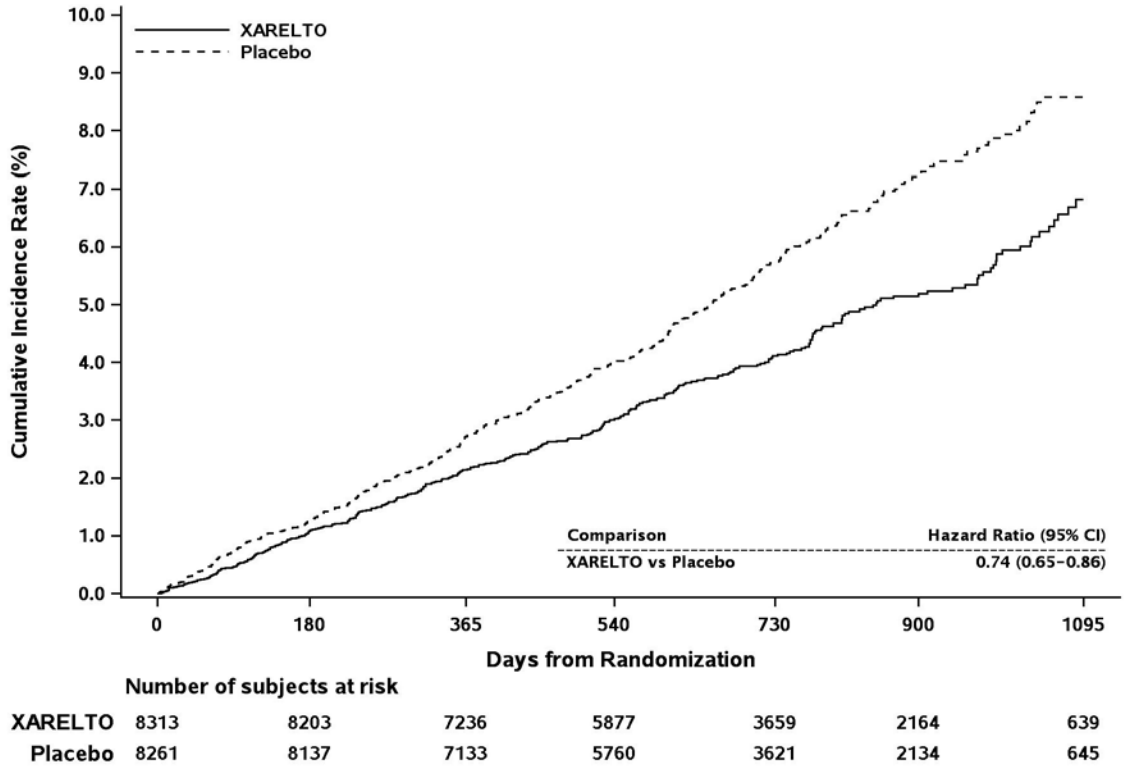
*All patients received aspirin 100 mg once daily as background therapy.

Table 19: Efficacy results from COMPASS CAD Population*

Event	XARELTO† N=8313		Placebo† N=8261		Hazard Ratio (95% CI)‡
	n (%)	Event Rate (%/year)	n (%)	Event Rate (%/year)	
Stroke, MI or CV death	347 (4.2)	2.2	460 (5.6)	2.9	0.74 (0.65, 0.86)
- Stroke	74 (0.9)	0.5	130 (1.6)	0.8	0.56 (0.42, 0.75)
- MI	169 (2.0)	1.1	195 (2.4)	1.2	0.86 (0.70, 1.05)
- CV death	139 (1.7)	0.9	184 (2.2)	1.1	0.75 (0.60, 0.93)
Coronary heart disease death, MI, ischemic stroke, acute limb ischemia	299 (3.6)	1.9	411 (5.0)	2.6	0.72 (0.62, 0.83)
- Coronary heart disease death§	80 (1.0)	0.5	107 (1.3)	0.7	0.74 (0.55, 0.99)
- Ischemic stroke	56 (0.7)	0.3	114 (1.4)	0.7	0.49 (0.35, 0.67)
- Acute limb ischemia#	13 (0.2)	0.1	27 (0.3)	0.2	0.48 (0.25, 0.93)
CV death,¶ MI, ischemic stroke, acute limb ischemia	349 (4.2)	2.2	470 (5.7)	3.0	0.73 (0.64, 0.84)
All-cause mortality	262 (3.2)	1.6	339 (4.1)	2.1	0.77 (0.65, 0.90)

* intention to treat analysis set, primary analyses.
† Treatment schedule: XARELTO 2.5 mg twice daily vs placebo. All patients received aspirin 100 mg once daily as background therapy.
‡ XARELTO vs. placebo.
§ Coronary heart disease death: death due to acute MI, sudden cardiac death, or CV procedure.
¶ CV death includes CHD death, or death due to other CV causes or unknown death.
# Acute limb ischemia is defined as limb-threatening ischemia leading to an acute vascular intervention (i.e., pharmacologic, peripheral arterial surgery/reconstruction, peripheral angioplasty/stent, or amputation).
CHD: coronary heart disease, CI: confidence interval; CV: cardiovascular; MI: myocardial infarction

Figure 10: Time to first occurrence of primary efficacy outcome (stroke, myocardial infarction, cardiovascular death) in the COMPASS CAD Population*



*All patients received aspirin 100 mg once daily as background therapy.
CI: confidence interval

14.7 Reduction of Risk of Major Thrombotic Vascular Events in Patients with PAD, Including Patients after Lower Extremity Revascularization due to Symptomatic PAD

The efficacy and safety of XARELTO 2.5 mg orally twice daily versus placebo on a background of aspirin 100 mg once daily in patients with PAD were evaluated in the COMPASS study (n=4996) and will be referred to as the COMPASS PAD population *[see Clinical Studies (14.6)]*.

The efficacy and safety of XARELTO were also evaluated for the reduction in the risk of the composite endpoint of myocardial infarction, ischemic stroke, cardiovascular death, acute limb ischemia (ALI), and major amputation of a vascular etiology in patients undergoing a lower extremity infrainguinal revascularization procedure due to symptomatic peripheral artery disease (PAD) in the double-blinded, placebo-controlled Vascular Outcomes studY of ASA alonG with rivaroxaban in Endovascular or surgical limb Revascularization for peripheral artery disease (PAD) trial (VOYAGER) [NCT02504216]. A total of 6,564 patients were equally randomized to

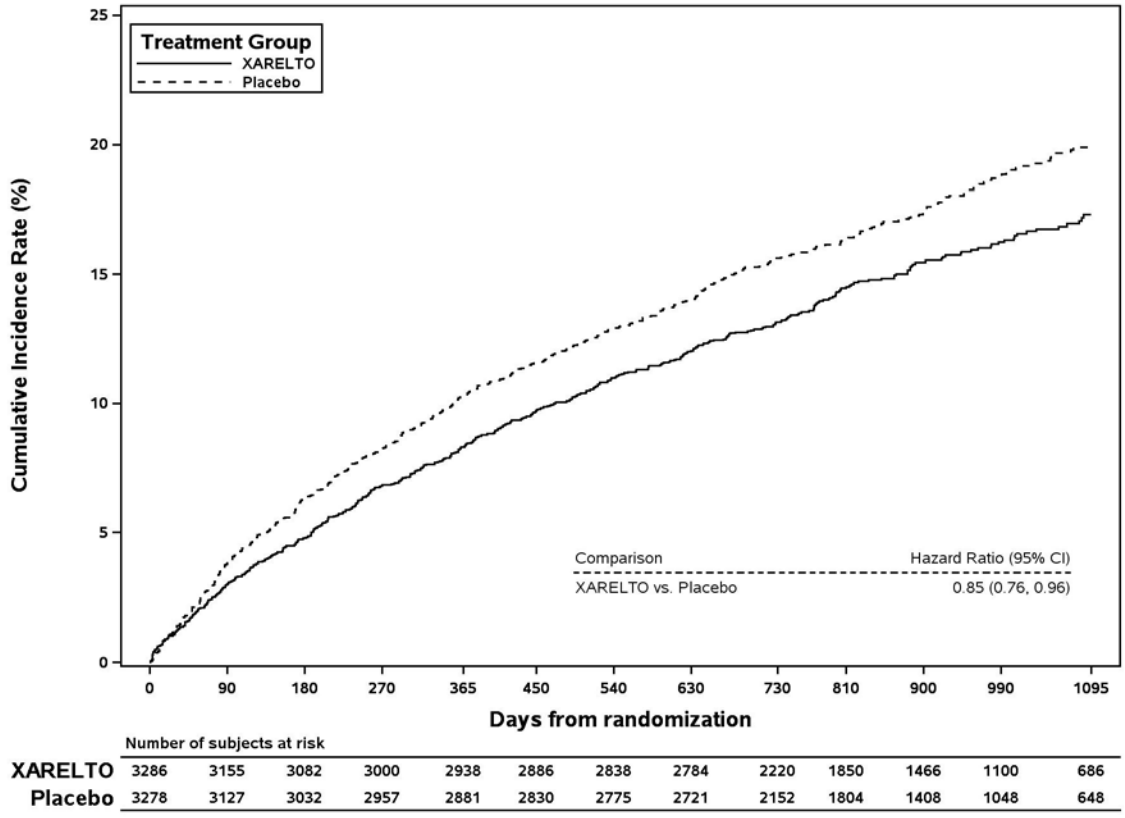
XARELTO 2.5 mg orally twice daily vs placebo on a background therapy of aspirin 100 mg once daily.

Eligible patients included adults who were at least 50 years of age with documented moderate to severe symptomatic lower extremity atherosclerotic PAD who had a successful peripheral surgical procedure and/or endovascular procedure with or without clopidogrel (up to a maximum of 6 months was allowed; median duration of therapy was 31 days). Patients had either a prior history of limb revascularization with ankle brachial index ≤0.85 or no prior history of limb revascularization with ankle brachial index ≤0.80. Patients in need of dual antiplatelet for >6 months, or any additional antiplatelet other than aspirin and clopidogrel, or oral anticoagulant, as well as patients with a history of intracranial hemorrhage, stroke, or transient ischemic attack (TIA), or patients with eGFR <15 mL/min were excluded.

The mean age was 67 years and 20% of the subject population was ≥75 years. Of the included patients, 35% had surgical revascularization, 47% had endovascular revascularization with clopidogrel, and 18% endovascular revascularization without clopidogrel. The median duration of follow-up was 30.8 months.

XARELTO 2.5 mg twice daily was superior to placebo in reducing the rate of the primary composite outcome of myocardial infarction, ischemic stroke, cardiovascular death, acute limb ischemia (ALI), and major amputation of a vascular etiology. The primary efficacy outcome and its components are provided in Table 20. The Kaplan-Meier plot for the primary efficacy outcome can be seen in Figure 11. The secondary efficacy outcomes were tested for superiority in a prespecified, hierarchical order and the first five of seven endpoints were significantly reduced in the rivaroxaban treatment arm (see Table 20). Compared to placebo during 10,000 patient-years of treatment, XARELTO would be expected to result in 181 fewer primary outcome events and 29 more TIMI major bleeding events, indicating a favorable balance of benefits and risks.

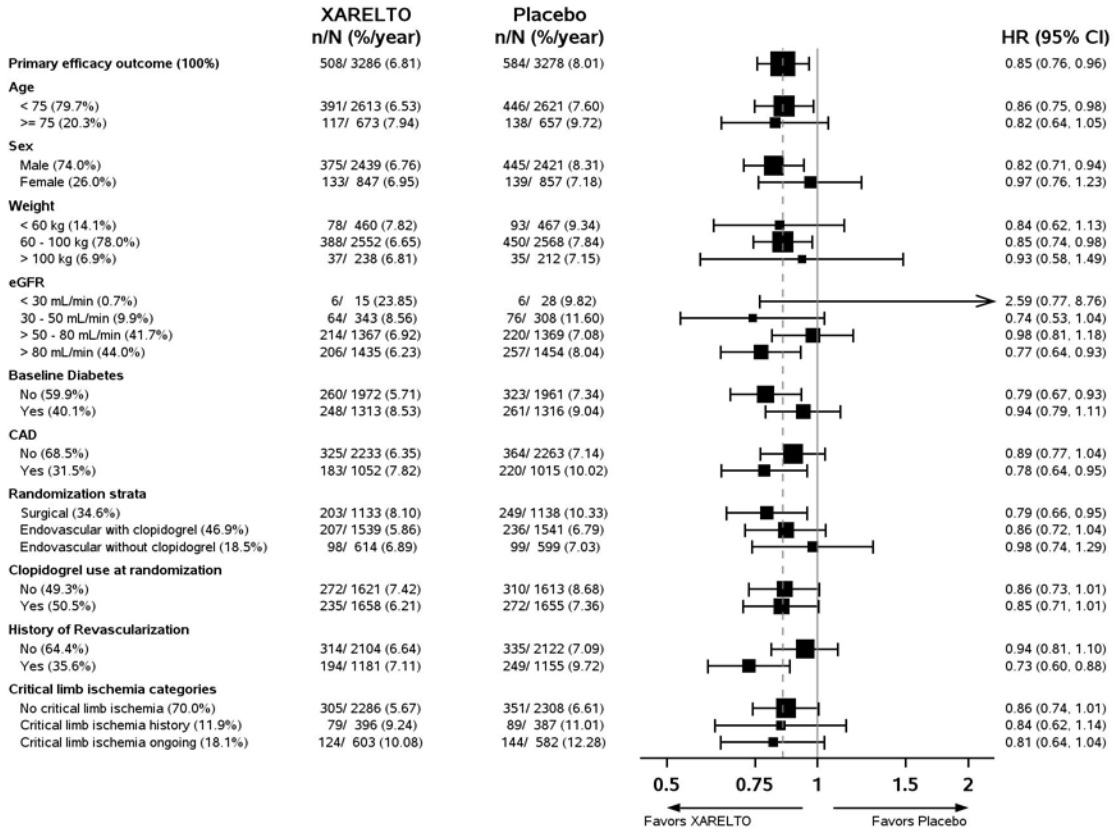
Figure 11: Time to First Occurrence of Primary Efficacy Outcome (Myocardial Infarction, Ischemic Stroke, Cardiovascular Death, Acute Limb Ischemia, Major Amputation due to Vascular Origins) in VOYAGER*



*All patients received aspirin 100 mg once daily as background therapy.

Figure 12 shows the risk of primary efficacy outcome across major subgroups. Subgroup analyses must be interpreted cautiously, as differences can reflect the play of chance among a large number of analyses. The primary efficacy endpoint generally shows homogeneous results across subgroups.

Figure 12: Risk of Primary Efficacy Outcome by Baseline Characteristics in VOYAGER (Intent-to-Treat Population)*



*All patients received aspirin 100 mg once daily as background therapy.

Table 20 provides the efficacy event rates for the prespecified endpoints in VOYAGER and similar endpoints in the COMPASS PAD population.

Table 20: Efficacy Results in VOYAGER (Intent-to-Treat Population) and COMPASS PAD

	VOYAGER			COMPASS PAD		
	XARELTO N=3286	**Placebo N=3278**	**Hazard Ratio (95% CI)* p-value†**	**XARELTO N=2492**	**Placebo N=2504**	**Hazard Ratio (95% CI)***
Outcome Components	**Event Rate (%/year)**			**Event Rate (%/year)**		
5-Component Outcome (Major thrombotic vascular events)‡	6.8	8.0	0.85 (0.76, 0.96) p=0.0085	3.4	4.8	0.71 (0.57, 0.87)
MI	1.7	1.9	0.88 (0.70, 1.12)	1.1	1.5	0.76 (0.53, 1.09)
Ischemic Stroke§	0.9	1.0	0.87 (0.63, 1.19)	0.5	0.9	0.55 (0.33, 0.93)
CV death¶	2.5	2.2	1.14 (0.93, 1.40)	1.4	1.7	0.82 (0.59, 1.14)
ALI	2.0	3.0	0.67 (0.55, 0.82)	0.4	0.8	0.56 (0.32, 0.99)
Major amputation of a vascular etiology#	1.3	1.5	0.89 (0.68, 1.16)	0.2	0.6	0.40 (0.20, 0.79)
VOYAGER Secondary Efficacy Outcomes[b]						
MI, ischemic stroke, CHD death,ß ALI, and major amputation due to vascular etiology	5.8	7.3	0.80 (0.71, 0.91) p=0.0008	2.8	4.2	0.66 (0.53, 0.83)
Unplanned index limb revascularization for recurrent limb ischemiaà	8.4	9.5	0.88 (0.79, 0.99) p=0.028	N/A	N/A	N/A
Hospitalization for a coronary or peripheral cause of a thrombotic nature#	3.5	4.8	0.72 (0.62, 0.85) p<0.0001	1.7	2.9	0.58 (0.44, 0.77)
MI, ischemic stroke, all-cause mortality, ALI, and major amputation due to vascular etiology	8.2	9.3	0.89 (0.79, 0.99) p=0.029	4.8	6.0	0.80 (0.67, 0.96)
MI, all-cause stroke, CV death, ALI, and major amputation due to vascular etiology	6.9	8.1	0.86 (0.76, 0.96) p=0.010	3.4	4.9	0.70 (0.57, 0.86)
All-cause mortality	4.0	3.7	1.08 (0.92, 1.27)	2.8	3.1	0.91 (0.72, 1.16)
VTE eventsè	0.3	0.5	0.61 (0.37, 1.00)	0.2	0.3	0.67 (0.30, 1.49)

Efficacy endpoints in COMPASS PAD were analysed according to the pre-specified endpoints in VOYAGER when applicable.

* XARELTO vs. placebo.

† Two-sided p-values

‡ Major thrombotic vascular event is the composite of MI, ischemic stroke, CV death, ALI, and major amputation of a vascular etiology.

§ Ischemic stroke for VOYAGER included stroke of uncertain/unknown etiology whereas COMPASS only included ischemic stroke.

¶ CV death includes Coronary Heart Disease death, or death due to other CV causes or sudden cardiac arrest and unknown death.

[#] Adjudicated events in VOYAGER and investigator reported events in COMPASS
[Þ] Secondary outcomes for VOYAGER were tested sequentially.
[ß] CHD death includes death due to sudden cardiac death, MI, or coronary revascularization procedure
[à] Unplanned index limb revascularization for recurrent limb ischemia was not captured in COMPASS study.
[è] Investigator reported in VOYAGER and adjudicated events in COMPASS
ALI=acute limb ischemia, CHD=coronary heart disease; CI=confidence interval, CV=cardiovascular; MI=myocardial infarction, VTE=venous thromboembolism.

16 HOW SUPPLIED/STORAGE AND HANDLING

XARELTO® (rivaroxaban) Tablets are available in the strengths and packages listed below:

- 2.5 mg tablets are round, light yellow, and film-coated with a triangle pointing down above a "2.5" marked on one side and "Xa" on the other side. The tablets are supplied in the packages listed:

  NDC 50458-577-60 Bottle containing 60 tablets

  NDC 50458-577-18 Bottle containing 180 tablets

  NDC 50458-577-10 Blister package containing 100 tablets (10 blister cards containing 10 tablets each)

- 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 50458-580-90 Bottle containing 90 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 50458-579-89	Bulk bottle containing 1000 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 room temperature between 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 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).

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 for initial treatment of 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 (2.1)]*.
- Advise patients who are at a continued risk of recurrent DVT and/or PE after at least 6 months of initial treatment, to take XARELTO 10 mg once daily with or without food *[see Dosage and Administration (2.1)]*.
- 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 (2.5)]*.
- 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 (2.5)]*.

- 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 *[see Dosage and Administration (2.4)]*.

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)]*.

Lactation

Advise patients to discuss with their physician the benefits and risks of XARELTO for the mother and for the child if they are nursing or intend to nurse during anticoagulant treatment *[see Use in Specific Populations (8.2)]*.

Females and Males of Reproductive Potential

Advise patients who can become pregnant to discuss pregnancy planning with their physician *[see Use in Specific Populations (8.3)]*.

Active Ingredient Made in Germany

Manufactured by:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from:
Bayer HealthCare AG
51368 Leverkusen, Germany

MEDICATION GUIDE
XARELTO® (zah-REL-toe)
(rivaroxaban)
tablets

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

XARELTO may cause serious side effects, including:

- **Increased risk of blood clots if you stop taking XARELTO.** People with atrial fibrillation (a type of irregular heart beat) that is not caused by a heart valve problem (non-valvular) 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.
- **Increased risk of bleeding.** XARELTO can cause bleeding which can be serious and may lead to death. This is because XARELTO is a blood thinner medicine (anticoagulant) that lowers blood clotting. During treatment with 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 have certain other medical problems.

  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
  - long-term (chronic) use of 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
  - 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 use in people with artificial heart valves.

XARELTO is not for use in people with antiphospholipid syndrome (APS), especially with positive triple antibody testing.

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 that is not caused by a heart valve problem. 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 DVT) or lungs (pulmonary embolism or PE)
- reduce the risk of blood clots happening again in people who continue to be at risk for DVT or PE after receiving treatment for blood clots for at least 6 months.
- help prevent a blood clot in the legs and lungs of people who have just had hip or knee replacement surgery.
- help prevent blood clots in certain people hospitalized for an acute illness and after discharge who are at risk of getting blood clots because of the loss of or decreased ability to move around (mobility) and other risks for getting blood clots and who do not have a high risk of bleeding.

XARELTO is used with low dose aspirin to:

- reduce the risk of serious heart problems, heart attack and stroke in people with coronary artery disease (a condition where the blood supply to the heart is reduced or blocked).
- reduce the risk of a sudden decrease in blood flow to the legs, major amputation, serious heart problems or stroke in people with peripheral artery disease (a condition where the blood flow to the legs is reduced) and includes people who have recently had a procedure to improve blood flow to the legs.

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

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 Medication Guide for a complete list of ingredients in XARELTO.

Before taking XARELTO, tell your doctor about all of your medical conditions, including if you:

- have or ever had bleeding problems
- have liver or kidney problems
- have antiphospholipid syndrome (APS)
- 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 during treatment with XARELTO. Taking XARELTO while you are pregnant may increase the risk of bleeding in you or in your unborn baby.
  - If you take XARELTO during pregnancy **tell your doctor** right away if you have any signs or symptoms of bleeding or blood loss. See **"What is the most important information I should know about XARELTO?" for signs and symptoms of bleeding.**

- are breastfeeding or plan to breastfeed. XARELTO can pass into your breast milk. Talk to your doctor about the best way to feed your baby during treatment with XARELTO.

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 over-the-counter medicines, vitamins, and herbal supplements.

Some of your other medicines may affect the way XARELTO works, causing side effects. 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
- erythromycin
- phenytoin
- St. John's wort
- ritonavir
- carbamazepine
- rifampin

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 may change your dose if needed.
- Your doctor will decide how long you should take XARELTO.
- XARELTO may need to be stopped for one or more days before any surgery or medical or dental procedure. Your doctor will tell you when to stop taking XARELTO and when to start taking XARELTO again after your surgery or procedure.
- If you need to stop taking XARELTO for any reason, talk to the doctor who prescribed XARELTO to you to find out when you should stop taking it. Do not stop taking XARELTO without first talking to the doctor who prescribes it to you.
- If you have difficulty swallowing XARELTO tablets whole, talk to your doctor about other ways to take XARELTO.
- 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.

If you take XARELTO for:

- **Atrial fibrillation that is not caused by a heart valve problem:**
  - 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 **1 or 2 times a day** as prescribed by your doctor.
  - For the **10 mg dose**, take XARELTO **with or without food.**
  - For the **15 mg and 20 mg doses**, take XARELTO **with food at the same time each day.**
  - If you miss a dose:
    - **If you take the 15 mg dose of XARELTO 2 times a day (a total of 30 mg of XARELTO in 1 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.
    - **If you 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.
- **Blood clots in people hospitalized for an acute illness:**
  - Take XARELTO 1 time a day, with or without food, while you are in the hospital and after you are discharged as prescribed by your doctor.

- 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.

- **Reducing the risk of serious heart problems, heart attack and stroke in coronary artery disease:**
  - Take XARELTO 2.5 mg 2 times a day with or without food.
  - If you miss a dose of XARELTO, take your next dose at your regularly scheduled time.
  - Take aspirin 75 to 100 mg once daily as instructed by your doctor.
- **Reducing the risk of a sudden decrease in blood flow to the legs, major amputation, serious heart problems or stroke in people with peripheral artery disease including those who have recently had a procedure to improve blood flow to the legs:**
  - Take XARELTO 2.5 mg 2 times a day with or without food.
  - If you miss a dose of XARELTO, take your next dose at your regularly scheduled time.
  - Take aspirin 75 to 100 mg once daily as instructed by your doctor.

What are the possible side effects of XARELTO?

XARELTO may cause serious side effects:

- See **"What is the most important information I should know about XARELTO?"**

The most common side effect of XARELTO was bleeding.

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 68ºF to 77ºF (20ºC to 25ºC).

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

General information about the safe and effective use of 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 symptoms that you have. It may harm them. You can ask your pharmacist or doctor for information about XARELTO that is written for health professionals.

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 2.5 mg tablets is Opadry® Light Yellow and contains: ferric oxide yellow, hypromellose, polyethylene glycol 3350, and titanium dioxide.

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.

Manufactured by: Janssen Pharmaceuticals, Inc. Titusville, NJ 08560 Licensed from: Bayer HealthCare AG 51368 Leverkusen, Germany

For more information go to www.XARELTO-US.com or call 1-800-526-7736.

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 08/2021

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NORMAN L STOCKBRIDGE
08/23/2021 04:45:45 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202439Orig1s035

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 202439/S-035

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Dvorsky, James
Eggers, Sara
Foss, David
Griffiths, LaShawn
Hutchins, Shawna
Kane, Bridget
Koh, William
Lackey, Leila
Matsuoka, Richard
Mehta, Hina
Monteleone, Michael V.
Rue, Bethany
Southworth, Mary Ross
Stockbridge, Norman L.
Straka, Maximilian
Zhang, Jialu

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202439Orig1s035

MULTI-DISCIPLINE REVIEW

MULTI-DISCIPLINARY COLLABORATIVE REVIEW

Application Type:	Efficacy Supplement
Application Number:	202439/S-035
Priority or Standard:	Standard
Received Date:	October 23, 2020
PDUFA Goal Date:	August 23, 2021
Division:	Division of Cardiology and Nephrology
Established Name:	rivaroxaban
Trade Name:	Xarelto
Applicant:	Janssen Pharmaceuticals Inc.
Formulation:	Tablet
Dosing Regimen:	2.5 mg qd
Proposed Indication:	XARELTO, in combination with aspirin, is indicated to reduce the risk of major thrombotic vascular events (myocardial infarction, ischemic stroke, acute limb ischemia, and major amputation of a vascular etiology) in patients who have recently undergone a lower extremity revascularization procedure due to symptomatic PAD.

Table of Contents

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1. Executive Summary and Conclusion

1.1 Regulatory Action

This memo serves as the primary statistical and clinical review and documents the Division's decision to expand the approval of rivaroxaban for use in patients with peripheral arterial disease.

Reviews were also conducted for medication errors (Straka and Mehta, 3/25/2021), the medication guide (Hutchins and Griffiths, 7/1/2021), and promotional aspects of labeling (Foss and Dvorsky, 7/13/2021). Any comments were considered in development of final labeling.

1.2 Benefit-Risk Assessment

Table 1: Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Patients with peripheral arterial disease typically have symptomatic lower limb ischemia and are at risk of limb loss. They are also apt to have systemic atherosclerotic disease. PAD is a progressive disease.	This is a serious disease with risk of limb loss or other cardiovascular events, including death.
Current Treatment Options	Patients with PAD are managed through a combination of surgical intervention and drug therapy. Patients with later-stage PAD may require surgical intervention, which can effectively address large vessel lesions near the bifurcation of the aorta, for example, but not multiple distal critical vessels. Rivaroxaban was approved in 2018 to reduce the risk of cardiovascular events in patients with CAD or PAD.	An unmet need exists for drug therapies to prevent limb loss, invasive vascular procedures, pain, and other cardiovascular events in PAD. Current labeling for rivaroxaban does not provide a clear claim for PAD independent of the claim for use in coronary artery disease.
Benefit	In VOYAGER-PAD, compared with placebo, rivaroxaban reduced the risk of non-fatal events, mostly acute limb ischemia, by about 15 events per 1000 years of treatment in patients with a recent revascularization procedure. With the exception of cardiovascular death, the other components of the primary endpoint (ischemic stroke, myocardial infarction, and major amputation) all demonstrated a benefit of rivaroxaban over placebo. A positive effect was also demonstrated for prevention of revascularization procedures.	Rivaroxaban reduces the risk of major complications of PAD by 15% in patients with a recent revascularization procedure.
Risk and Risk Management	Rivaroxaban is an anticoagulant, and its risks are primarily increased hemorrhage. In VOYAGER, there were about 2 excess serious, non-fatal hemorrhages per 1000 years of treatment. Other, less serious, bleeding events were also elevated.	This risk is managed according to guidelines for use of rivaroxaban for other indications.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	In VOYAGER, there were 3 per 1000 patient-years excess cardiovascular mortality as well as an increase in fatal hemorrhages and all-cause mortality. However, in COMPASS, there was a reduction in mortality of about the same magnitude.	There is probably little effect of rivaroxaban on mortality in this setting.

1.2.1 Conclusion Regarding Benefit-Risk

Treatment of patients with PAD proximal to a revascularization procedure was associated with about 15 fewer non-mortal cardiovascular events per 1000 patient-years compared to placebo. Two-thirds of this benefit was in reduction of ALI, which had to satisfy 5 criteria: (a) sudden worsening of symptoms, (b) leading to hospitalization, (c) demonstrated pulse deficit, (d) pain, pallor paresthesia, or paralysis, and (e) confirmatory imaging or invasive intervention.

In terms of harm, there were 2 per 1000 patient-years excess non-fatal hemorrhages that were more than hemoglobin or hematocrit drops. Across COMPASS and VOYAGER together, there is little effect on mortality.

Quantitative benefit-risk analyses performed by the Decision Support and Analysis Staff and the Applicant tend to support a conclusion that the benefits of rivaroxaban for PAD outweigh the risks (review by Lackey and Rue). For some models, this conclusion was sensitive to the weight placed on different outcomes — particularly the weight placed on ALI — and to beliefs about the relevance of the COMPASS mortality findings for PAD patients proximal to a revascularization procedure. The process of specifying the quantitative models and reviewing and interpreting the results informed the review team's understanding of the decision problem and the regulatory benefit-risk assessment and decision.

2. Interdisciplinary Collaborative Review

2.1 Regulatory context

Among others, rivaroxaban has a claim "to reduce the risk of major cardiovascular events in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD)" on the basis of COMPASS, in which 27395 subjects (4996 with PAD [ABI < 0.9] alone or 3297 with PAD plus CAD) were randomized to placebo, rivaroxaban 2.5 mg, or rivaroxaban 5 mg on a background of aspirin 100 mg and followed for about 2 years. In the overall population, rivaroxaban was associated with about 7/1000 patient-years fewer stroke plus MI plus CV death events (2.5-mg dose) and about 4 per 1000 patient-years fewer deaths from any cause. Effects on the composite in subgroups with PAD only or CAD only were similar and individually statistically different from placebo.

In COMPASS, only about ¼ of the PAD subjects had any prior revascularization, whereas VOYAGER-PAD, reviewed here, enrolled a PAD population shortly after revascularization.

2.2 Approach to the Review

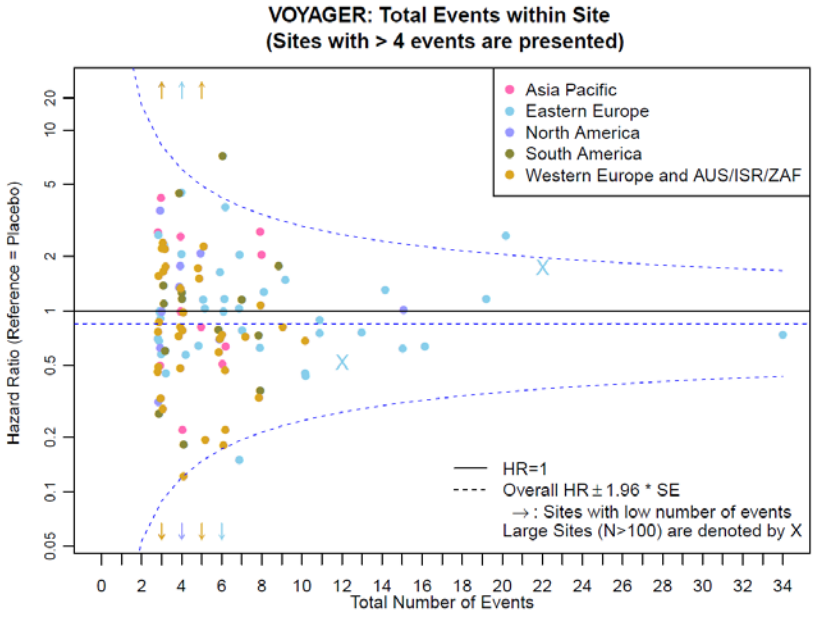
This was a joint statistical and clinical review.

The review focuses on VOYAGER. In addition, we considered the PAD population from COMPASS (referred to as COMPASS PAD) to be a separate study that contributes to the overall findings for the

PAD indication. Because COMPASS was previously submitted for review, the study will not be further reviewed.

We looked for outlier sites that might have disproportionately affected the results (Figure 1); there were none, and no site inspections were requested or performed.

Figure 1 Funnel Plot of Estimated Hazard Ratio by Total Events by Site



Source: Statistical Reviewer

2.3 Trial Design

VOYAGER-PAD was conducted between August 18, 2015 (first subject randomized) and November 27, 2019 (last subject randomized) at 548 sites in Western and Eastern Europe, North and South America, and Asia-Pacific.

Subjects were age >50, within 10 days of having undergone an index revascularization for symptomatic atherosclerotic lower limb peripheral arterial disease (clinical, anatomic, and hemodynamic criteria), excluding patients with prior revascularization within 10 days of the index procedure or with planned DAPT (clopidogrel only plus aspirin) of more than six months. Prior coronary artery disease was permitted.

Subjects were randomized 1:1 to rivaroxaban 2.5 mg twice daily (bid) and matching placebo. Randomization was stratified by use of surgery vs endovascular procedure with clopidogrel vs endovascular procedure without clopidogrel, with blocks by country to ensure balance.

All subjects received background aspirin 100 mg once daily. Clopidogrel use was discouraged beyond 30 days of surgical revascularization or 60 days for some devices.

Study visits were at planned at 1, 3, and 6 months, and then every 6 months.

The study was event-driven, planned to accrue at least 1015 events, sized with at least 90% power, testing at two-sided alpha of 0.05, to detect at least 20% relative risk reduction. Based on these specifications, the study anticipated randomizing at least 6500 subjects assuming the control event rate of 7.5% per year, duration of enrollment of 18 months with a minimum follow-up of two years for the last randomized subject. In addition, the rate of lost-to-follow-up was 1.5% annually and permanent treatment discontinuation rates was 5.5% for the first year, 8% for second year, 12% for third year, and 8% every half year afterwards.

The global protocol was amended twice after initiation; both amendments dealt mostly with clarifying what constituted a revascularization endpoint (secondary endpoint). The trial description is based on the final protocol.

The statistical analysis plan was amended twice after the original draft and analysis was based on version 3.0 dated July 24, 2019. The amendments for each version were done to be consistent with the protocol versions. A supplement to the SAP dated April 17, 2020 was included in the submission. The efficacy cut-off date (ECOD) for the primary efficacy analysis was September 08, 2019.

Trial was under the direction of an Executive Committee. An International Steering Committee facilitated communications between investigators and the Executive Committee. A data monitoring committee was independent of other committees and reviewed unblinded safety data, focusing on bleeding events. The trial conduct appears to be adequate based on the meeting minutes submitted. Endpoint events were adjudicated (9-member panel with initial 2 reviewers and committee chair for disputes); the process appears reasonable, although not useful.

The sponsor provided debarment certification and financial disclosure information; neither raise issues of interpretation for VOYAGER-PAD.

The primary endpoint was major thrombotic events—MI, ischemic stroke, CV death, acute limb ischemia (ALI), or major amputation. The Kaplan Meier curve was used to describe the cumulative incidence rates over time. The event rate per was reported based on the total number of events divided by the total patient years (p-y) in the study.

The primary analysis for the primary endpoint was time to first event in the ITT population, assessed using a stratified log-rank test and a two-sided alpha=0.05. The point estimate and 95% Wald-based confidence intervals (CI) were reported using the stratified Cox proportional hazards model. An interim analysis was planned with a 2-sided alpha=0.001 at 67% of events based on the Haybittle-Peto monitoring rule; no adjustment was made to the final alpha for multiple testing.

Hierarchical secondary endpoints were time to first (a) MI, ischemic stroke, coronary heart disease death, ALI, or major amputation, (b) unplanned index limb revascularization, (c) hospitalization for coronary or peripheral thrombotic event, (d) MI, ischemic stroke, all-cause death, ALI or major amputation, (e) MI, any stroke, CV death, ALI, or major amputation, (f) all-cause death, and (g) VTE. The statistical analysis for these endpoints was similar to that for the primary endpoint.

Subgroup analyses were conducted within levels of the subgroup category for the primary efficacy endpoint using the same statistical method for the primary endpoint. To assess for effect modification of subgroup and treatment, the likelihood ratio test was applied by testing the full Cox proportional hazards (PH) model including treatment, subgroup, and interaction of subgroup and treatment,

stratified by type of procedure and clopidogrel use with the Cox PH model without the subgroup and treatment interaction.

For the safety endpoints, similar statistical methods were used for the Thrombolysis in Myocardial Infarction (TIMI) Major and related bleeding endpoints. In addition, to facilitate description of benefit risk, risk differences on the absolute scale are presented when necessary. The 95% CI for the risk differences is based on Sahai and Kurshid 1996.[1] The number needed to treat (NNT) or number needed to harm are calculated based on the reciprocal of risk differences on the absolute scale.

Adverse events by the main system organ class, with at least 0.1% higher on the rivaroxaban arm on the absolute scale, were reported based on the proportion of patients with at least one event on or after the date of randomization until 7 days following discontinuation of randomized study treatment.

The Applicant pre-specified sensitivity analyses to investigate the potential impact of missing follow-up on the primary efficacy analysis. In addition, the Agency requested an analysis based on a retrieved dropout imputation. In this approach, the hazard rate was estimated based on the follow-up of subjects who had discontinued randomized treatment but continued to be followed for efficacy endpoint. The Weibull survival model was used to estimate the hazard rate within each arm. Then, the missing follow-up for subjects who were censored prior to ECOD was imputed based on the hazard rate sampled from the distribution obtained from the retrieved dropout. The process was repeated to generate 1000 imputed datasets. For each imputed dataset, the same primary statistical analysis was applied to obtain the HR, 95% CI, p-values. Rubin's rule was used to combine these results.

2.4 Study Results

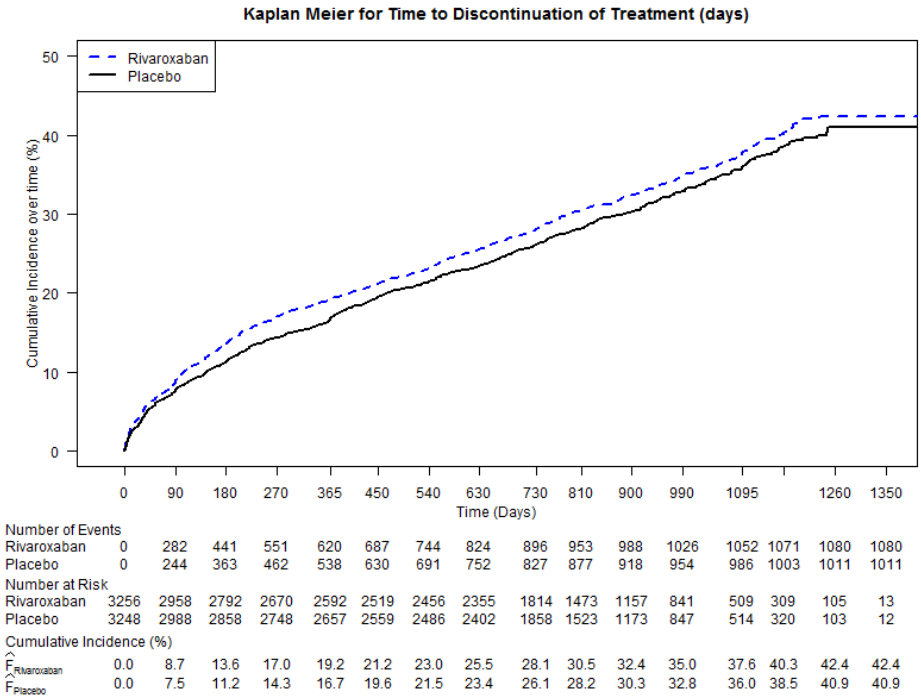
2.4.1 Subject Disposition

Total enrollment was 6564. Mean follow-up was 731 days on rivaroxaban and 746 days on placebo. Although vital status was ascertained in more than 99% of cases, permanent study drug discontinuation was high—33% on rivaroxaban and 31% on placebo. Reasons captured for permanent discontinuation of rivaroxaban/placebo through ECOD[2] were similar on rivaroxaban and placebo, with a numerical higher number of subjects discontinuing for bleeding reasons (Table 9). The temporal pattern of discontinuations is shown in Figure 2.

[1] Sahai H, Kurshid A. Statistics in epidemiology: methods techniques and applications. CRC Press 1996

[2] Subjects who discontinued randomized treatment continue to be followed for key efficacy outcomes unless they withdrew informed consent to be followed for further efficacy outcomes.

Figure 2 Kaplan Meier for Time to Permanent Discontinuation of Randomized Treatment through ECOD based on Safety Analysis Set



Abbreviations: ECOD=efficacy cut-off date
Source: Statistical Reviewer

The small difference between the groups in timing of discontinuation appears to have happened at the 3-month visit.

The rates and temporal distributions of discontinuations of aspirin were similar to Figure 2 for rivaroxaban.

Study site and data management were reasonable. The most common protocol violation was failure to exclude subjects with history of intracranial hemorrhage, stroke, or transient ischemic attack (TIA) (1.1%).

Blinded adjudication packages were provided to the adjudication committee; they reviewed only cases identified by the sites.

About 62% of subjects received concomitant clopidogrel. The next most common concomitant antiplatelet/anticoagulant drug was enoxaparin, at about 7% in both groups. About 39% received antidiabetic therapy.

A sampling of the coding of adverse events to PTs revealed no problems.

2.4.2 Subject Demographics and Other Characteristics

Baseline characteristics can be seen in the forest plot of results and are balanced (Table 10, Table 11, Table 12). On average, subjects were 67 years of age. A total of 74% of the subjects were male; 81% were White, and 2% of the subjects were Black. Only 8% of the randomized subjects were from US.

Baseline disease characteristics were balanced between arms. In particular, the distribution of baseline eGFR values were similar between arms, with 76% of the subjects having an eGFR greater than 60 mL/min/1.73m^2.

2.4.3 Efficacy Results

Primary endpoint results are shown below. In VOYAGER-PAD, a total of 508 (event rate of 68 per 1000 p-y) and 584 (80 per 1000 p-y) subjects in the rivaroxaban and placebo arm respectively experienced a primary composite endpoint, with an estimated adjusted hazard ratio (HR) of 0.85 (95% CI: 0.76, 0.96; p-value=0.0085). The results for the individual components, except for CV death, were consistent with the primary efficacy findings. The individual component for ALI was nominally significant. For CV death, there was a numerical trend towards greater risk (HR: 1.14; 95% CI: 0.93, 1.40) for subjects on rivaroxaban compared to placebo.

Table 2 Primary Endpoint Results and Time to First Individual Components

	Events (Event rate per 1000 p-y)		HR (95% CI)	P-value
	Rivaroxaban N=3286	Placebo N=3278		
Composite	508 (68)	584 (80)	0.85 (0.76, 0.96)	0.009
MI	131 (17)	148 (19)	0.88 (0.70, 1.12)	
Ischemic stroke	71 (9)	82 (10)	0.87 (0.63, 1.19)	
CV death	199 (25)	174 (22)	1.14 (0.93, 1.40)	
ALI	155 (20)	227 (30)	0.67 (0.55, 0.82)	
Amputation	103 (13)	115 (15)	0.89 (0.68, 1.16)	

Abbreviations: MI=myocardial infarction; CV=cardiovascular; ALI=acute limb ischemia; HR=hazard ratio; CI=confidence interval; p-y=patient years

Source: Study report p 133; confirmed by review team

Investigator-reported and adjudicated event rates are presented in the Table 3. Based on the investigator reported events, the HR for the primary composite endpoint was 0.92 (95% CI: 084, 1.02; p=0.1). The sponsor attributes the large discrepancy in reported and adjudicated rates of ALI to liberal reporting instructions.

Table 3 Primary Endpoint Results for Adjudicated and Investigator Reported Events

	Events (Event rate per 1000 p-y)			
	Adjudicated		Investigator-reported	
	Rivaroxaban	Placebo	Rivaroxaban	Placebo
Composite	508 (68)	584 (80)	794 (115)	849 (125)
MI	131 (17)	148 (19)	106 (14)	121 (15)
Ischemic stroke	71 (9)	82 (10)	81 (10)	89 (11)
CV death	199 (25)	174 (22)	195 (24)	165 (20)
ALI	155 (20)	227 (30)	516 (73)	586 (84)
Amputation	103 (13)	115 (15)	79 (10)	100 (13)

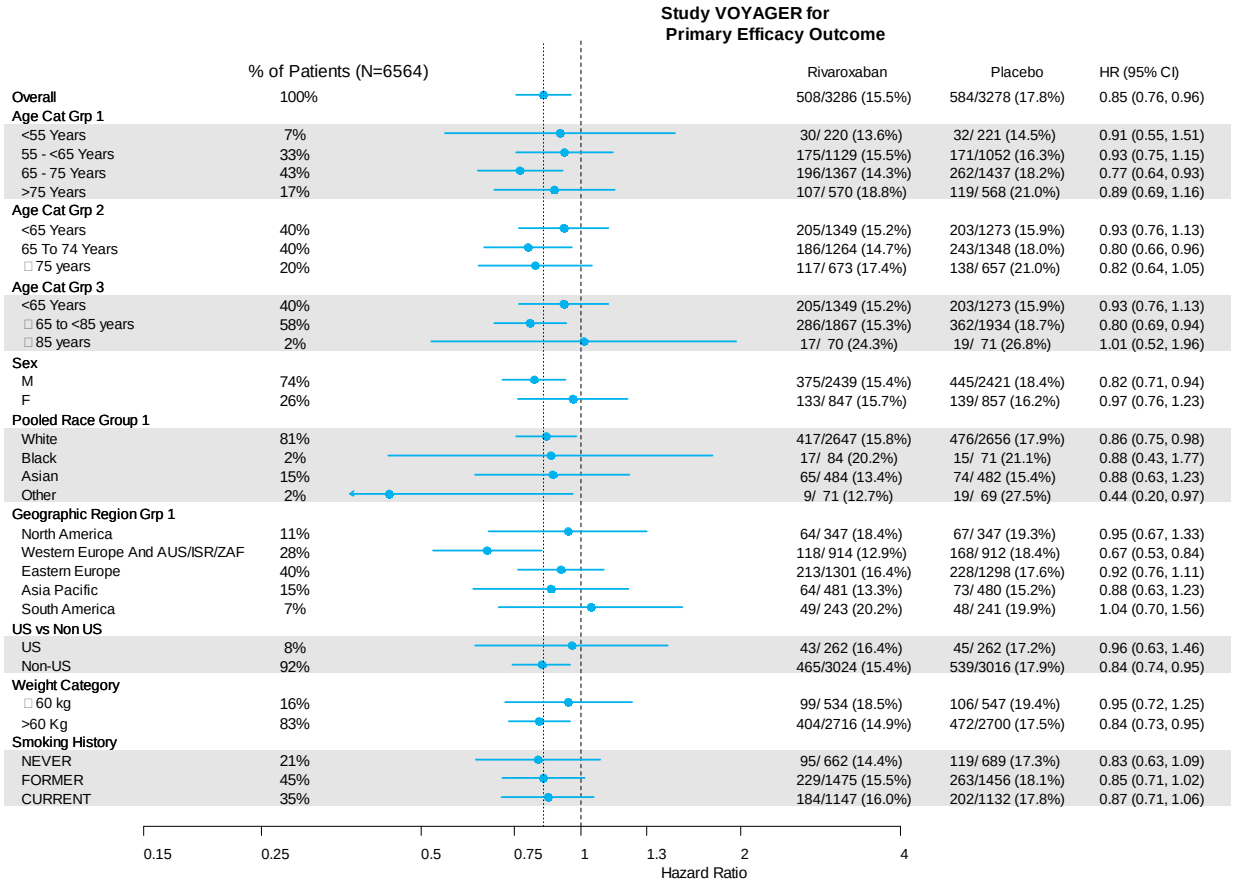
Abbreviations: MI=myocardial infarction; CV=cardiovascular; ALI=acute limb ischemia; p-y=patient years

Source: Study report, pp. 133 and 285; confirmed by review team

A total of 97 subjects did not have complete ascertainment of primary efficacy endpoint or were censored much earlier than the efficacy cut-off date (Table 13). The Applicant conducted sensitivity analyses to evaluate the impact of missing follow-up on the primary efficacy results. Using a retrieved dropout approach, the results remained consistent with the conclusion of the primary efficacy endpoint. In summary, the primary efficacy results were robust to missing data assumptions.

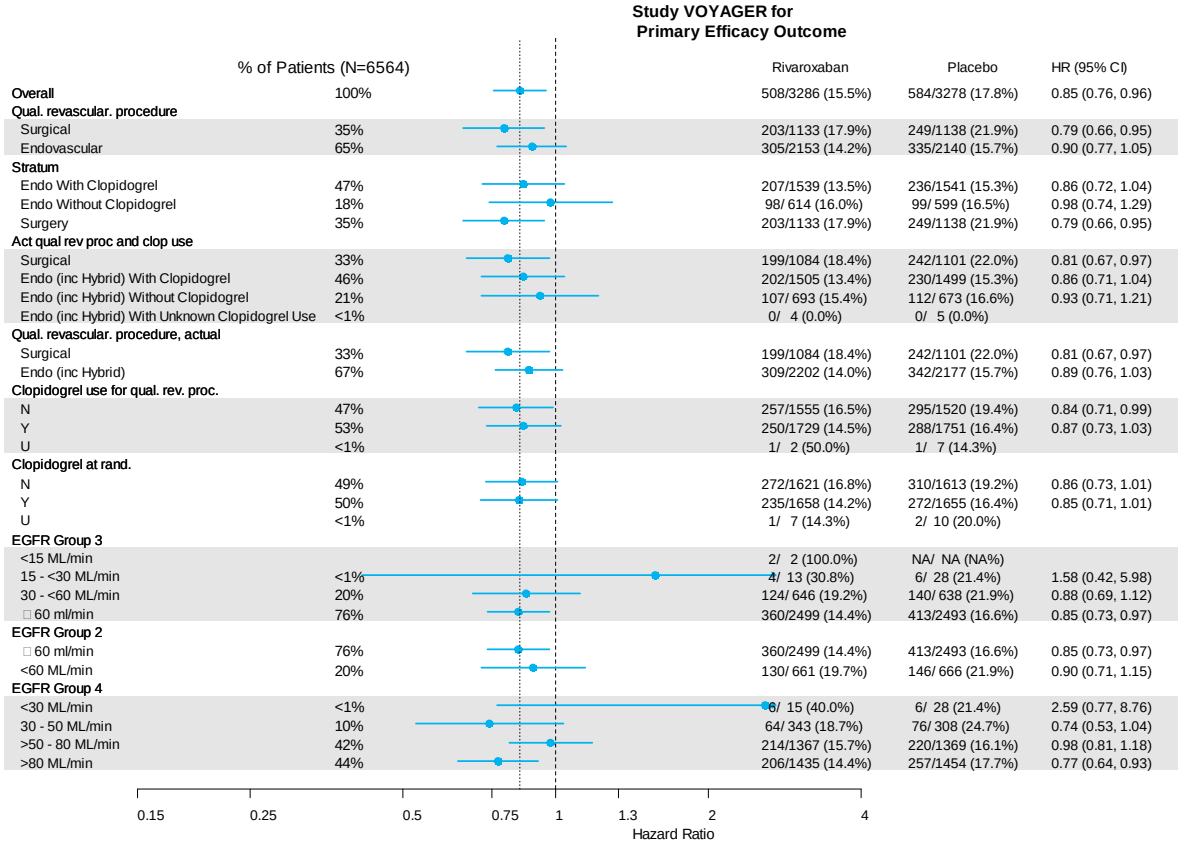
Forest plots (split) for primary results by prespecified baseline subgroups are shown below (Figure 3, Figure 4, Figure 5). In summary, the subgroup findings by key demographic, geographic, and clinical subgroups of interest were consistent with the findings of the primary composite endpoint in direction of benefit towards rivaroxaban relative to placebo arm. Effect modification was nominally statistically significant for subgroup variable for prior history of limb revascularization (p=0.036).

Figure 3 Forest Plot of Primary Endpoint by Baseline Characteristics (VOYAGER-PAD) 1 of 3



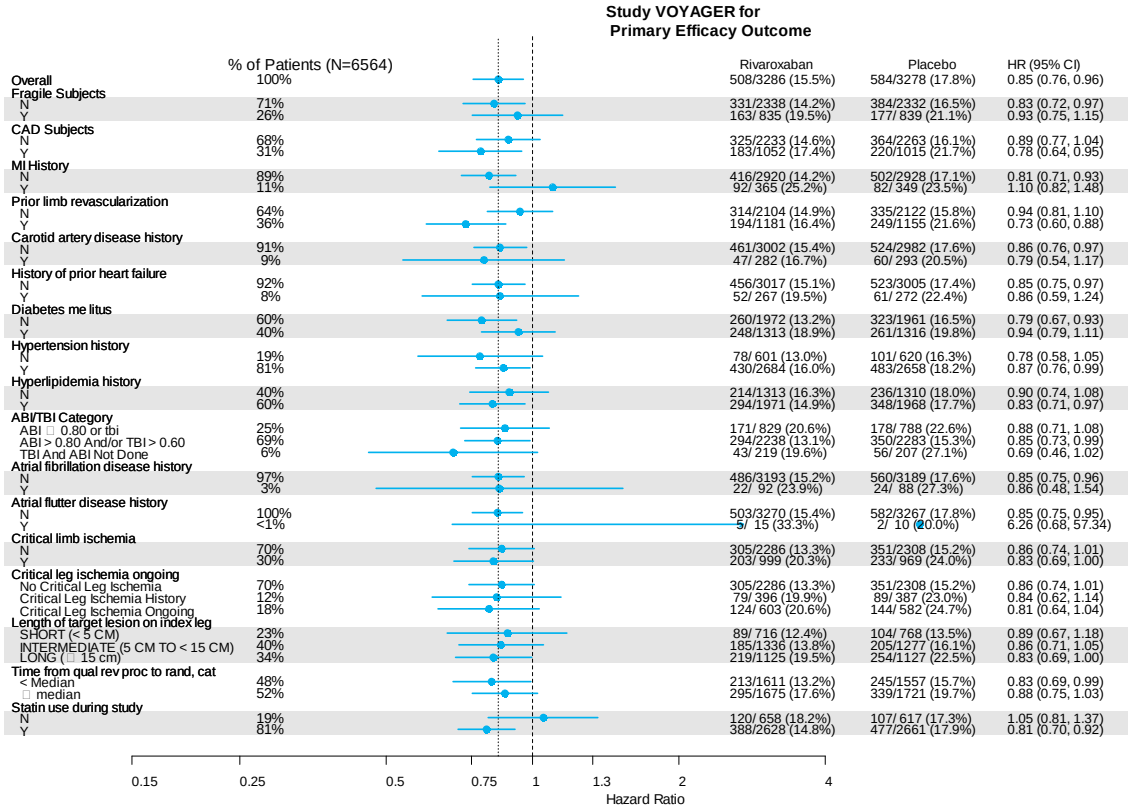
Abbreviations: HR=hazard ratio; CI=confidence interval
Source: Statistical Reviewer

Figure 4 Forest Plot of Primary Endpoint by Baseline Characteristics (VOYAGER-PAD) 2 of 3



Abbreviations: eGFR=estimated glomerular filtration rate; Endo; endovascular
Source: Statistical Reviewer

Figure 5 Forest Plot of Primary Endpoint by Baseline Characteristics (VOYAGER-PAD) 3 of 3



Abbreviations: ABI=ankle brachial index; TBI=toe brachial index; CAD=coronary artery disease; MI=myocardial infarction
Source: Statistical Reviewer

The results for the pre-specified secondary endpoints are in Table 4. Key secondary endpoints listed 1-5 were statistically significant per the specified multiplicity procedure. For all-cause death, the event rate was 40 per 1000 p-y and 37 per 1000 p-y on rivaroxaban arm and placebo arm respectively, with a numerical trend towards greater risk of all-cause death (HR: 1.08; 95% CI: 0.92, 1.27; p=0.34) comparing subjects on rivaroxaban with subjects on placebo.

Table 4 Results for the Pre-specified Secondary Endpoints

		Events (Events per 1000 p-y)		HR (95% CI)	P-value
		Rivaroxaban N=3286	Placebo N=3278		
1	MI, ischemic stroke, coronary heart disease death, ALI, or major amputation	433 (58)	528 (73)	0.80 (0.71, 0.91)	0.001
2	Unplanned index limb revascularization [1]	584 (84)	655 (95)	0.88 (0.79, 0.99)	0.03
3	Hospitalization for coronary or peripheral thrombotic event	262 (35)	356 (48)	0.72 (0.62, 0.85)	<0.001

4	MI, ischemic stroke, all-cause death, ALI or major amputation	614 (82)	679 (93)	0.89 (0.79, 0.99)	0.03
5	MI, any stroke, CV death, ALI, or major amputation	514 (69)	588 (81)	0.86 (0.76, 0.96)	0.01
6	All-cause death	321 (40)	297 (37)	1.08 (0.92, 1.27)	0.34
7	VTE	25 (3)	41 (5)	0.61 (0.37, 1.00)	0.049

1: Events were investigator-reported
Abbreviations: MI=myocardial infarction; ALI=acute limb ischemia; HR=hazard ratio; CV=cardiovascular; VTE=venous thromboembolic
Source: Statistical Reviewer

2.4.4 Safety Results

Safety data are presented on 6504 subjects, excluding 30 subjects in each group who never received study drug.

Overall, 50% of subjects on rivaroxaban reported an adverse event vs 49% on placebo. Fewer than 9% in both groups discontinued because of an adverse event; the between-group difference was <1%. For no MedDRA SOC did the rate on rivaroxaban exceed the rate on placebo by 1%.

For SAEs, the rates were 33% in both treatment groups. For no SOC did the rate on rivaroxaban exceed the rate on placebo by 1%.

Vital status was available for >99% of randomized subjects.

Analyses of adverse events were undertaken using the MAED application using a window for all adverse events with an onset date on or after the date of randomization until 7 days following permanent discontinuation of randomized treatment. Results by SOC are reported for AEs where the rate on rivaroxaban exceeded the rate on placebo arm by at least 0.1% (Table 5).

Table 5 Common Adverse Events by SOC, VOYAGER-PAD[3]

	Rivaroxaban (N = 3286)		*Placebo (N = 3278)*	
SOC	*Events*	*Subjects*	*Events*	*Subjects*
Blood and lymphatic system disorders	70	70 (2.1%)	52	52 (1.6%)
Gastrointestinal disorders	284	200 (6.1%)	261	193 (5.9%)
Product issues	10	10 (0.3%)	1	1 (<0.1%)
Renal and urinary disorders	93	82 (2.5%)	82	68 (2.1%)

Abbreviations: SOC=systems organ class
Source: Table 1 of information request dated June 04, 2021, confirmed by review team

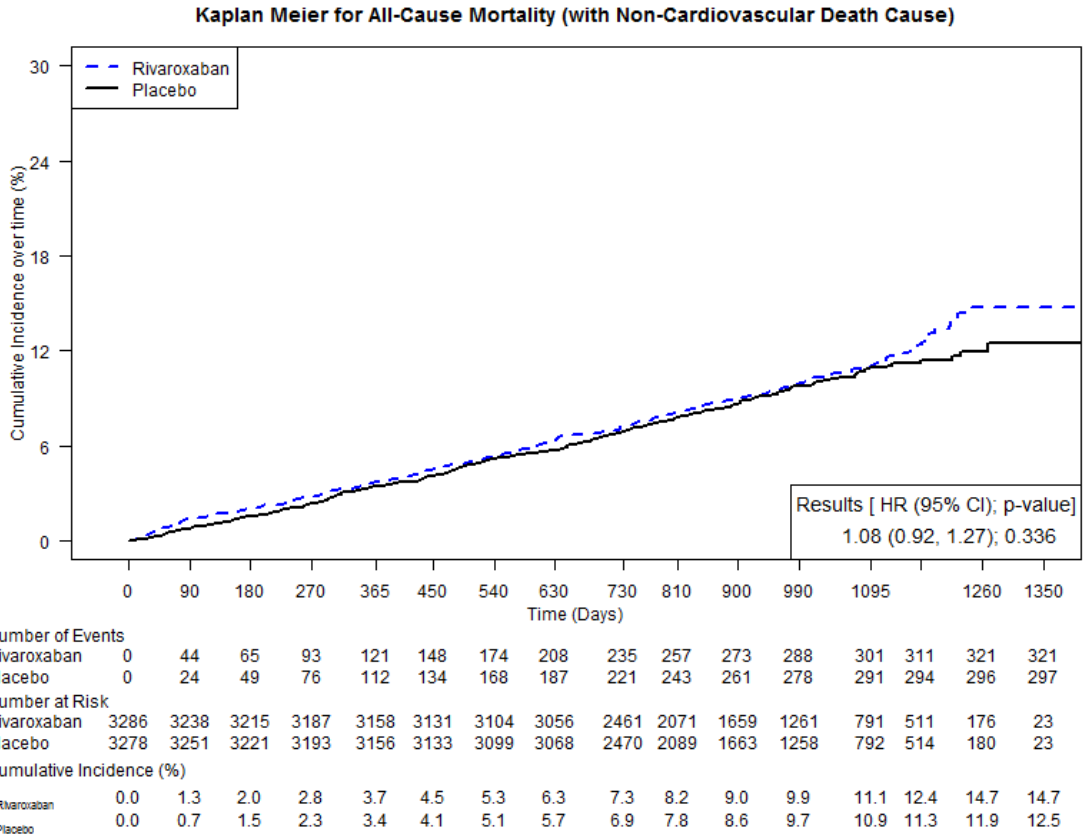
The only broad standardized MedDRA query (SMQ) with a rate on rivaroxaban exceeding the rate on placebo by at least 0.5% were related to hemorrhage or dehydration, the excess being 0.5-0.7% in various groupings. No narrow SMQ met the 0.5% test.

[3] MAED analysis on ae.xpt, sorted by risk difference and restricted to events where the rate on rivaroxaban exceeded the rate on placebo by at least 0.1%.

No preferred term (PT) met the 0.5% test. The rate of peripheral artery stenosis was higher on rivaroxaban (by ~0.5%). The rate of anemia was also higher on rivaroxaban (0.4%).

The K-M curves for all-cause mortality are shown in Figure 6. Divergence only appears at three years, when only about 20% of subjects remain in study. These characteristics contribute to the conclusion that this is a spurious finding.

Figure 6 Kaplan Meier for Time to All-Cause Mortality



Abbreviation: HR=hazard ratio; CI=confidence interval
Source: Statistical Reviewer confirmed and reproduced the figure

Adjudicated causes of death are summarized in the Table 6:

Table 6 Adjudicated Causes of Death

	Rivaroxaban (N = 3286)	*Placebo (N = 3278)*
Any	9.8%	9.1%
CV + unknown	4.2	3.7
Coronary heart disease	2.6	2.4
Sudden	1.7	1.5
Acute MI	0.5	0.6
..Non-coronary[4]	1.6	1.3
Unknown	1.9	1.6
Non-cardiovascular	3.7	3.8

Abbreviation: CV=cardiovascular; MI=myocardial infarction
Source: Death dataset

The excess deaths in the rivaroxaban arm are distributed among various cardiovascular causes. It is not seen among non-cardiovascular causes, including hemorrhagic, where it might have been more plausible.

There are few deaths in various deep vein thrombosis (DVT) studies, except for MAGELLAN, conducted in 7998 subjects hospitalized for mostly CV illnesses. For all-cause mortality within 2 days of discontinuation, the rates were 1.8% on rivaroxaban and 2.0% on enoxaparin. In ROCKET-AF,[5] among 14236 subjects randomized, all-cause mortality was 8.8% on rivaroxaban and 9.4% on warfarin. Positive controls in MAGELLAN and ROCKET-AF complicate their interpretation, although both positive controls have established benefits in high-risk cardiovascular conditions. Perhaps the most probative data are from ATLAS-ACS-2 TIMI 51,[6] in which 15506 subjects were randomized to placebo or rivaroxaban 2.5 or 5 mg. All-cause mortality was 2.9% on rivaroxaban 2.5 mg and 4.5% on placebo. Cardiovascular mortality was 2.7% on rivaroxaban and 4.1% on placebo. Thus, the adverse trend in CV death is not seen in the much larger safety database of rivaroxaban studies, which included many subjects with cardiovascular risk factors.

Deaths in COMPASS—all-cause, cardiovascular, or non-cardiovascular—trended favorably overall on rivaroxaban 2.5 mg but adversely in the PAD subgroup with no known CAD. A comparison of endpoint and mortality rates by CAD status is shown in the Table 7 for the VOYAGER-PAD and corresponding subsets in COMPASS:

[4] Heart failure, shock, thromboembolic
[5] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202439Orig1s000RocketAFReanalysis.pdf
[6] Mega JL, Braunwald E, Murphy SA, Plotnikov AN, Burton P, Kiss RG, Parkhomenko A, Tendera M, Widimsky P, Gibson CM. Rivaroxaban in patients stabilized after a ST-segment elevation myocardial infarction: results from the ATLAS ACS-2-TIMI-51 trial (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis In Myocardial Infarction-51). J Am Coll Cardiol. 2013 May 7;61(18):1853-9. doi: 10.1016/j.jacc.2013.01.066. Epub 2013 Mar 7. PMID: 23500262.

Table 7 Event Rates (per 1000 p-y) for Primary Efficacy Endpoint, CV Death, and All-Cause Mortality, Studies VOYAGER-PAD and COMPASS

	Events per 1000 patient-years							
	VOYAGER-PAD				COMPASS			
	-CAD		+CAD		-CAD		+CAD	
	Riv 2.5 N=3002	Pbo N=2982	Riv 2.5 N=282	Pbo N=293	Riv 2.5 N=2492	Pbo N=2504	Riv 2.5 N=1656	Pbo N=1641
Primary	68	79	73	92	30	49	33	51
CV mortality	25	21	21	25	14	15	14	19
All-cause mortality	39	33	42	46	29	31	25	33

Abbreviation: Pbo=placebo; Riv=rivaroxaban
Source: CSR

Event rates are consistently higher in VOYAGER-PAD than in COMPASS, probably reflective of the intervention proximal to randomization. Having recognized CAD in addition to PAD conveys little additional risk; one has to suspect that many have CAD, recognized or not. The adverse trend in mortality seen in VOYAGER-PAD is confined to subjects without recognized CAD; the findings are essentially the inverse in the smaller subset with recognized CAD, and there is no adverse mortality finding at all in COMPASS.

The VOYAGER study report contains many exploratory analyses of the mortality finding, none of which are reviewed here. We conclude that the finding of adverse mortality in VOYAGER-PAD is unlikely to be reliable.

TIMI Major bleeding (fatal within 7 d, intracranial, or Hgb decrease of 5 g/dL or HCT decrease of 15%) was reported by 1.9% (9.6 per 1000 p-y) on rivaroxaban and 1.4% (6.7 per 1000 p-y) on placebo (Table 8). This difference based on the relative (HR: 1.42; 95% CI: 0.97, 2.1) or absolute scale (Risk Difference: 29 per 1000 p-y; 95% CI: -2, 60) is not statistically significant. There were 6 fatal hemorrhage events in each treatment group. Intracranial hemorrhage rates were 0.4% on rivaroxaban and 0.5% on placebo. TIMI Major events by hemoglobin/hematocrit drop were 7.1 per 1000 p-y on rivaroxaban and 3.6 per 1000 p-y on placebo.

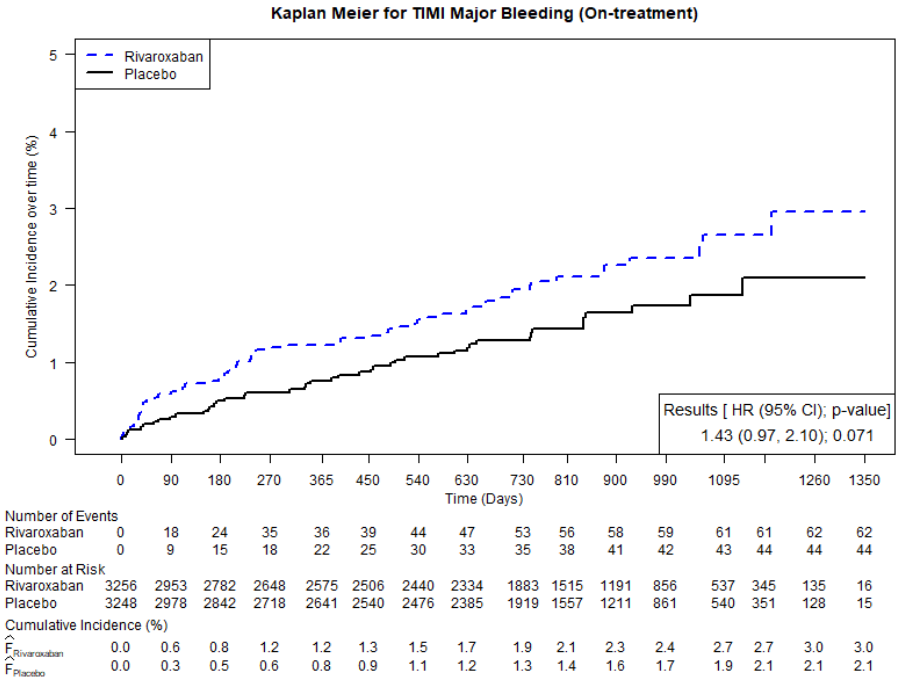
Table 8 Event Rates for On-treatment TIMI Major bleeding (and subcategories) and Related Safety Outcomes

	Events (Event Rate per 1000 patient-years)	
	Rivaroxaban N=3256	Placebo N=3248
TIMI Major	62 (9.6)	44 (6.7)
Fatal	6 (0.9)	6 (0.9)
Intracranial bleeding	13 (2.0)	17 (2.6)
Hgb ↓5 g/dL	46 (7.1)	24 (3.6)
TIMI Minor	46 (7.1)	31 (4.7)
Requiring medical attention	316 (51)	192 (30)
TIMI Minimal	138 (22)	91 (14)
Any TIMI Major/Minor/Minimal	239 (38)	158 (25)

Abbreviations: TIMI=Thrombolysis in Myocardial Infarction; Hgb=hemoglobin
Source: Statistical Reviewer reproduced table from clinical study report

Figure 7 shows the K-M curves for TIMI major bleeding events, illustrating a constant increase in incidence rate over time after initiation for the placebo arm. For the rivaroxaban arm, the risk appears to higher after initiation and then appears relatively constant in rate throughout the study.

Figure 7 Kaplan Meier Curve for Time to TIMI Major Bleeding, On Treatment



Abbreviations: TIMI=Thrombolysis in Myocardial Infarction; HR=hazard ratio; CI=confidence interval
Source: Statistical Reviewer

Figure 14 (appendix) shows the KM curves for subjects who discontinued randomized treatment for bleeding reasons superimposed with the KM for any TIMI Major/Minor/Minimal events. There was a

higher rate of discontinuation for bleeding reasons in rivaroxaban arm compared to placebo. The proportion of subjects who discontinued after a bleeding event was generally higher on rivaroxaban than on placebo, but the rates in both groups are low—about 2%.

2.5 Assessment of Efficacy and Safety

- Missing data

The presence of missing data can affect the interpretation of the study results. In summary, the study was adequately conducted. Patients were adequately followed, with 1.5% of the subjects having incomplete follow-up of the primary efficacy endpoint. A retrieved dropout multiple imputation analysis did not change the overall conclusions. Therefore, we conclude that the primary efficacy results were robust to missing data.

- Substantial evidence of effectiveness

The applicant conducted the pivotal, multi-center study VOYAGER to provide evidence of rivaroxaban as a treatment for patients with symptomatic PAD soon after a lower-extremity revascularization procedure. Previously, the COMPASS study was submitted to support the current approved indication in patients with CAD or PAD. COMPASS studied a chronic PAD patient population with high risk of ischemic events. Therefore, we considered the chronic PAD patient population from COMPASS (referred to as COMPASS-PAD) to provide independent support on efficacy and safety findings.

The primary results for VOYAGER were strong (0.85; 95% CI: 0.76, 0.96; p-value=0.009) and study conduct was adequate with 1.5% of the patients with incomplete follow-up of the primary endpoint. The components of the efficacy endpoints except for CV death trended favorably towards rivaroxaban compared to placebo. The findings from the key secondary endpoints were significant and in favor of rivaroxaban compared to placebo except for all-cause mortality.

In a retrospective analysis of COMPASS-PAD population according to VOYAGER efficacy endpoints, the findings were consistent with the results observed in VOYAGER except for all-cause death and CV death. All-cause death and CV death trended favorably towards rivaroxaban based on the COMPASS-PAD population. These findings were not only supportive but consistent with the current findings in VOYAGER notwithstanding the lack of pre-specification, exploratory nature, retrospective re-analysis, potential differences in capturing or reporting of endpoints.

- Mortality imbalance and plausibility of mortality risk

In VOYAGER, the unexpected trend towards higher rates of CV death and all-cause mortality towards rivaroxaban compared to placebo was of concern. These observations were not nominally significant. As noted in Section 2.4.4, active control studies evaluating rivaroxaban were not observed to have a trend towards higher mortality rates on rivaroxaban compared to the active control. These comparisons are limited due to differences in study design. We also reviewed any current literature of relevant placebo-controlled randomized studies in other disease populations (ATLAS-ACS-2), including reviewing a retrospective analysis of COMPASS looking at the CAD, PAD, and CAD +PAD population. This adverse trend in mortality was not observed in these studies.

2.6 Conclusions

Rivaroxaban has been approved in multiple disease populations (namely patients with nonvalvular atrial fibrillation, deep vein thrombosis, pulmonary embolism, coronary artery disease). The safety profile is known and well-documented.

Based on the VOYAGER findings and additional evaluation from the COMPASS-PAD population, the totality of evidence demonstrated the efficacy of rivaroxaban in treatment of patients with PAD despite the unexpected mortality findings.

3. Labeling Recommendations

The approved indication was to reduce the risk of major cardiovascular events in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD), and we have now developed separate CAD and PAD indications. This provides a clearer way of organizing the indication according to the patient population. The CAD indication is supported by COMPASS, using the population with or without known PAD.

We presented the key results of VOYAGER based on the prespecified primary and key secondary endpoints and exclude the p-values for endpoints that did not meet the multiplicity hierarchy. We included results from a retrospective analysis of comparable VOYAGER efficacy endpoints from the COMPASS-PAD population together with VOYAGER since the patient population provides additional support for the overall indication in PAD patients.

We acknowledge such approach can be considered misleading in several ways, namely:

1) A total of 19% of the patient population in COMPASS had both CAD and PAD and are reported in data supporting the CAD indication and PAD indication. The conclusions are unchanged regardless of whether these subjects are considered part of the PAD subgroup.

2) The COMPASS-PAD results reported in the PAD indication are based on the primary and secondary endpoints prespecified in VOYAGER. Differences in data capture (such as adjudicated vs investigator-reported), or lack of adequate capturing of data could bias interpretation of the results. These issues can be mitigated by appropriate description in labeling.

3) These additional analyses are conducted post-hoc and retrospectively. It should be noted that in a setting when the drug does not have any effect on any of its endpoints, there is a high chance of false positive findings by conducting a retrospective exploratory analysis of the clinical trial. However, the COMPASS study met its primary and key secondary hypothesis, as well as meeting its primary hypothesis in CAD, PAD, and CAD+PAD subgroups. In addition, rivaroxaban is approved for an indication in the CAD or PAD patient population based on COMPASS. Therefore, in the light of a positive, adequate and well-controlled and conducted study, presentation of findings according to endpoints is reasonable.

Therefore, in light of these issues 1-3, suitable description can be included to clarify that results from COMPASS-PAD as reported together with VOYAGER were done retrospectively to prevent any misleading interpretation.

See also the Executive Summary.

4. Appendix

Table 9 Disposition for Completion/Discontinuation of Randomized Treatment

	Rivaroxaban N=3286	Placebo N=3278	All N=6564
Did not initiate treatment	30 (<1%)	30 (<1%)	60 (<1%)
Completed Randomized Treatment	2176 (66%)	2237 (68%)	4413 (67%)
Stopped on ECOD on or after ECOD – 2 days while alive	2076 (63%)	2115 (65%)	4191 (64%)
Stopped within 2 days of death	100 (3%)	122 (3.7%)	222 (3.4%)
Discontinued Randomized Treatment	1080 (33%)	1011 (31%)	2091 (32%)
Patient's Wish	240 (7.3%)	233 (7.1%)	473 (7.2%)
Non-Bleeding Adverse Event	218 (6.6%)	213 (6.5%)	431 (6.6%)
Efficacy Outcome Event	166 (5.1%)	183 (5.6%)	349 (5.3%)
Bleeding	133 (4%)	53 (1.6%)	186 (2.8%)
DAPT Or Systemic Anticoagulation	69 (2.1%)	86 (2.6%)	155 (2.4%)
Administrative Reasons	74 (2.3%)	67 (2%)	141 (2.1%)
Surgical Intervention	49 (1.5%)	46 (1.4%)	95 (1.4%)
Subject Error	46 (1.4%)	28 (<1%)	74 (1.1%)
Invasive Procedure	34 (1%)	38 (1.2%)	72 (1.1%)
Other	19 (<1%)	36 (1.1%)	55 (<1%)
Physician Decision	23 (<1%)	21 (<1%)	44 (<1%)
Reasons Were Missing	8 (<1%)	3 (<1%)	11 (<1%)
Hospitalization	1 (<1%)	4 (<1%)	5 (<1%)

Counts and percentages relative to N are presented.
Abbreviations: DAPT=Dual antiplatelet therapy; ECOD=efficacy cut-off date
Source: Statistical Reviewer

Table 10 Baseline Demographics and Other Characteristics

Characteristics	Rivaroxaban N=3286	Placebo N=3278	All N=6564
Age [1]	67 (8.5) 49 - 93	67 (8.5) 50 - 95	67 (8.5) 49 - 95
< 65	1349 (41%)	1273 (39%)	2622 (40%)
[65, 75)	1264 (38%)	1348 (41%)	2612 (40%)
[75, 85)	603 (18%)	586 (18%)	1189 (18%)
≥ 85	70 (2%)	71 (2%)	141 (2%)
Male	2439 (74%)	2421 (74%)	4860 (74%)
Female	847 (26%)	857 (26%)	1704 (26%)
Race			
White	2647 (81%)	2656 (81%)	5303 (81%)
Black	84 (3%)	71 (2%)	155 (2%)
Asian	484 (15%)	482 (15%)	966 (15%)
Other	2 (<1%)	7 (<1%)	9 (<1%)

Characteristics	Rivaroxaban N=3286	Placebo N=3278	All N=6564
Not Reported	69 (2%)	62 (2%)	131 (2%)
Ethnicity			
Hispanic	261 (8%)	267 (8%)	528 (8%)
Not Hispanic	3025 (92%)	3011 (92%)	6036 (92%)
Region			
US	262 (8%)	262 (8%)	524 (8%)
Outside of US	3024 (92%)	3016 (92%)	6040 (92%)
Baseline Weight (kg) [1]	76 (16.0) 31 - 150	76 (16) 32 - 160	76.2 (16.0) 31 - 160
< 60	534 (16%)	547 (17%)	1081 (16%)
≥ 60	2716 (83%)	2700 (82%)	5416 (83%)
Missing	36 (1%)	31 (<1%)	67 (1%)
Baseline Height (cm) [1]	169.5 (9.3) 133 - 200	169.4 (9.1) 129 - 197	169.5 (9.2) 129 – 200

Counts and percentages in parenthesis are presented except for 1 where mean and standard deviations in parenthesis on the first row and minimum – maximum on the second row.
Source: Statistical Reviewer

Table 11 Baseline Disease Characteristics

	Rivaroxaban N=3286	Placebo N=3278	All N=6564
Baseline eGFR (mL/min/1.73m^2) [1]	78.6 (25.8) 9 – 619 (n=3160)	78.2 (23.4) 18 – 237 (n=3159)	78.4 (24.6) 9 – 619 (n=6319)
<15	2 (<1%)	0 (<1%)	2 (<1%)
[15, 30)	13 (<1%)	28 (<1%)	41 (<1%)
[30, 60)	646 (20%)	638 (19%)	1284 (20%)
≥ 60	2499 (76%)	2493 (76%)	4992 (76%)
Baseline ABI[1]	0.9 (0.2) 0 - 2	0.9 (0.2) 0 - 2	0.9 (0.2) 0 – 2
< 0.8	796 (24%)	752 (23%)	1548 (24%)
≥ 0.8	2208 (67%)	2261 (69%)	4469 (68%)
Missing	282 (9%)	265 (8%)	547 (8%)
Baseline TBI[1]	0.6 (0.2) 0 - 1	0.6 (0.3) 0 - 2	0.6 (0.2) 0 – 2
< 0.8	34 (1%)	37 (1%)	71 (1%)
≥ 0.8	31 (<1%)	26 (<1%)	57 (<1%)
Missing	3221 (98%)	3215 (98%)	6436 (98%)
Baseline LDL (mmol/L) [1]	101.8 (41.1) 16 - 327 (N=779)	101.6 (41.5) 8 – 303 (N=751)	101.7 (41.3) 8 – 327 (N=1530)

	Rivaroxaban N=3286	Placebo N=3278	All N=6564
Days from qualifying revascularization procedure to rand (N) [1]	5.0 (2.8) 1 - 11 (N=3286)	5.1 (2.8) 1 – 23 (N=3278)	5.0 (2.8) 1 – 23 (N=6564)
Days from qualifying revascularization procedure to start of study drug[1]	5.2 (2.9) 1 – 39 (N=3256)	5.3 (3.4) 1 – 62 (N=3248)	5.2 (3.2) 1 – 62 (N=6504)
Smoking History			
Current Smoker	1147 (35%)	1132 (35%)	2279 (35%)
Former Smoker	1475 (45%)	1456 (44%)	2931 (45%)
Never Smoker	662 (20%)	689 (21%)	1351 (21%)
Missing	2 (<1%)	1 (<1%)	3 (<1%)
Baseline Stratification			
Endovascular with Clopidogrel	1539 (47%)	1541 (47%)	3080 (47%)
Endovascular with Clopidogrel	614 (19%)	599 (18%)	1213 (18%)
Surgery	1133 (34%)	1138 (35%)	2271 (35%)
Actual type of qualifying procedure and clopidogrel use at randomization			
Endovascular incl. hybrid with clopidogrel	1505 (46%)	1499 (46%)	3004 (46%)
Endovascular incl. hybrid without clopidogrel	693 (21%)	673 (21%)	1366 (21%)
Endovascular incl. hybrid / Unknown use of clopidogrel	4 (<1%)	5 (<1%)	9 (<1%)
Surgical with clopidogrel	153 (5%)	156 (5%)	309 (5%)
Surgical without clopidogrel	928 (28%)	940 (29%)	1868 (28%)
Surgical / Unknown use of clopidogrel	3 (<1%)	5 (<1%)	8 (<1%)

1: First row: Mean and standard deviation in parenthesis; Second row: Minimum – maximum; Third row; Total number of observations (if presented)
All rows presented are counts and percentages relative to N unless otherwise specified
Source: Statistical Reviewer

Table 12 Medical History at Randomization

	Rivaroxaban N=3286	Placebo N=3278	All N=6564
Carotid artery disease	282 (9%)	293 (9%)	575 (9%)
Baseline Anemia	105 (3%)	113 (3%)	218 (3%)
History of MI	365 (11%)	349 (11%)	714 (11%)
History of Hyperlipidemia	1971 (60%)	1968 (60%)	3939 (60%)
History of Hypertension	2684 (82%)	2658 (81%)	5342 (81%)
Prior limb revascularization	1181 (36%)	1155 (35%)	2336 (36%)
Prior Ischemic amputation	174 (5%)	168 (5%)	342 (5%)

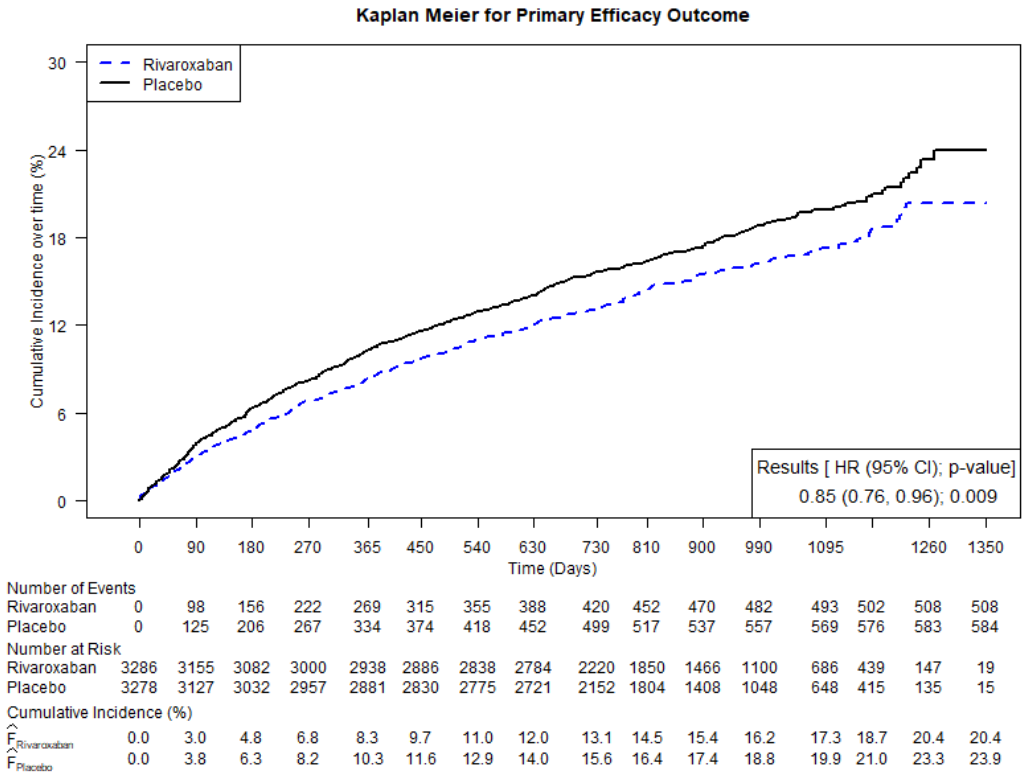
Counts and percentages relative to N are presented.
Abbreviations: MI=myocardial infarction
Source: Statistical Reviewer

Table 13 Characterization of Subjects with Incomplete Follow-up of Primary Efficacy Endpoint

	Rivaroxaban N=3286	Placebo N=3278	Total N=6564
Subjects with incomplete follow-up until efficacy cut-off date	49 (1.5%)	48 (1.5%)	97 (1.5%)
Consent withdrawn/Object to future data collection	28 (<1%)	28 (<1%)	56 (<1%)
Consent withdrawn/Did not object to future data collection	5 (<1%)	7 (<1%)	12 (<1%)
Lost to follow-up with no death prior to ECOD	3 (<1%)	5 (<1%)	8 (<1%)
Lost to follow-up with non CV-death prior to ECOD	13 (<1%)	8 (<1%)	21 (<1%)
Total follow-up time based on all subjects (years)	89.3	89.1	178
Total missing follow-up time in years	7461	7291	14752

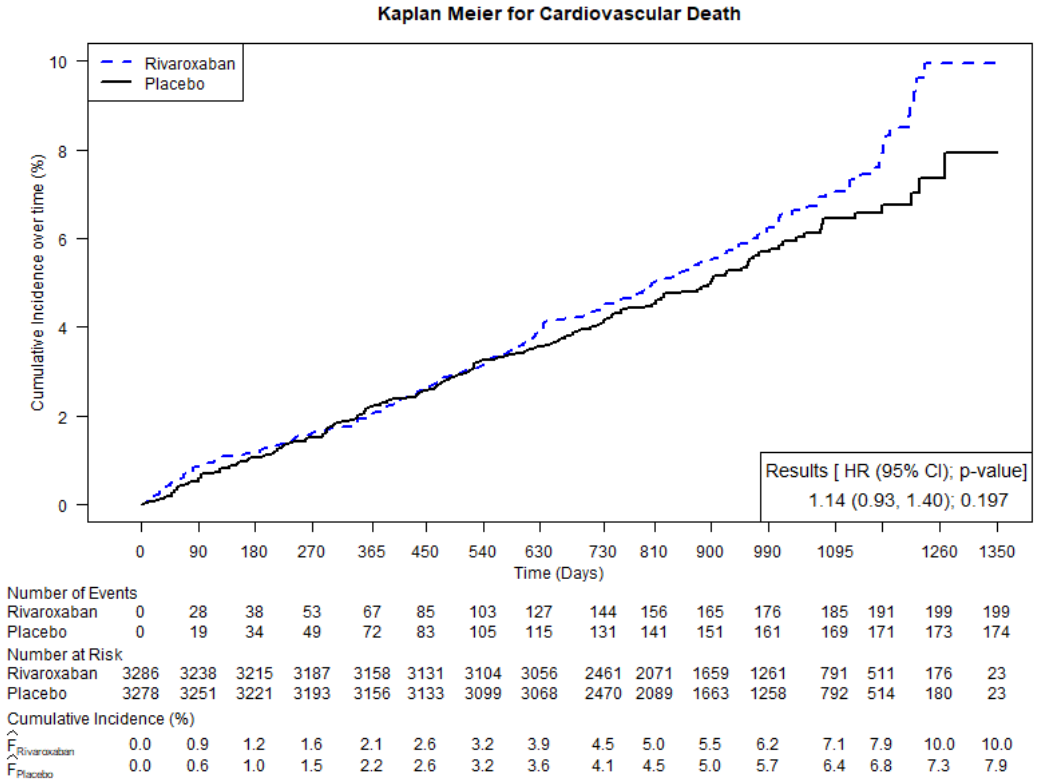
Abbreviations: CV=cardiovascular; ECOD=efficacy cut-off date
Source: Statistical Reviewer

Figure 8 Kaplan Meier Curve for Primary Efficacy Endpoint



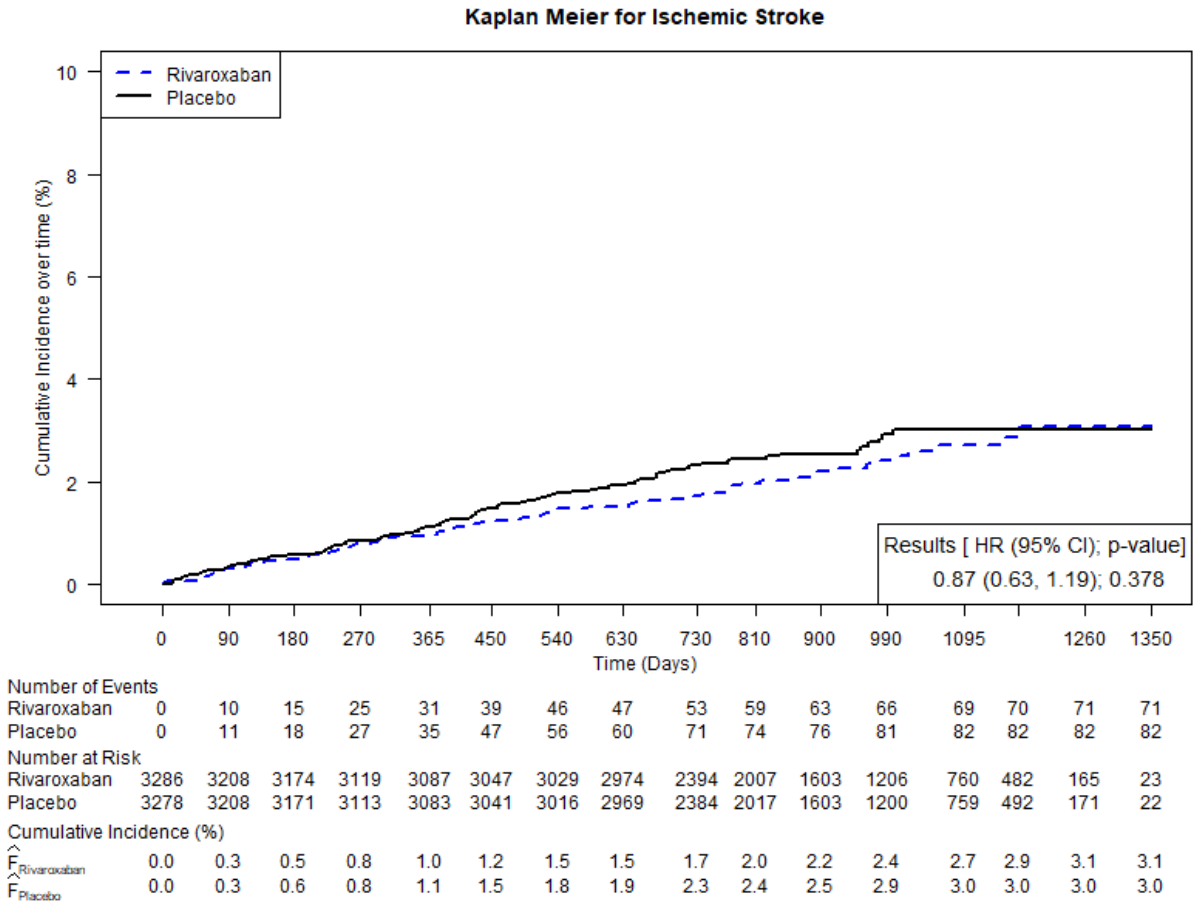
Abbreviations: HR=hazard ratio; CI=confidence interval
Source: Statistical Reviewer

Figure 9 Kaplan Meier Curve for Time to CV Death



Abbreviations: HR=hazard ratio; CI=confidence interval
Source: Statistical Reviewer

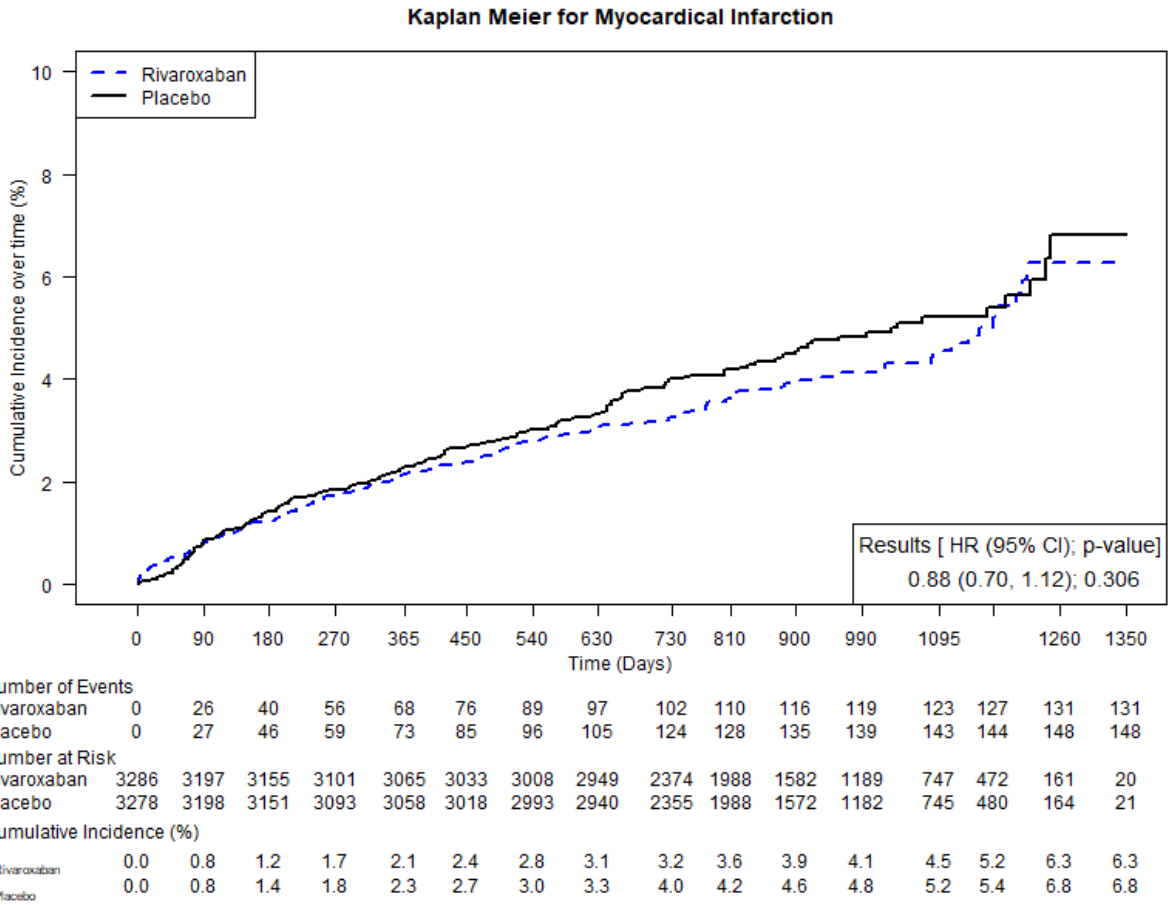
Figure 10 Kaplan Meier Curve for Time to Ischemic Stroke



Number of Events																
Rivaroxaban	0	10	15	25	31	39	46	47	53	59	63	66	69	70	71	71
Placebo	0	11	18	27	35	47	56	60	71	74	76	81	82	82	82	82
Number at Risk																
Rivaroxaban	3286	3208	3174	3119	3087	3047	3029	2974	2394	2007	1603	1206	760	482	165	23
Placebo	3278	3208	3171	3113	3083	3041	3016	2969	2384	2017	1603	1200	759	492	171	22
Cumulative Incidence (%)																
$\hat{F}_{Rivaroxaban}$	0.0	0.3	0.5	0.8	1.0	1.2	1.5	1.5	1.7	2.0	2.2	2.4	2.7	2.9	3.1	3.1
$\hat{F}_{Placebo}$	0.0	0.3	0.6	0.8	1.1	1.5	1.8	1.9	2.3	2.4	2.5	2.9	3.0	3.0	3.0	3.0

Abbreviations: HR=hazard ratio; CI=confidence interval
Source: Statistical Reviewer

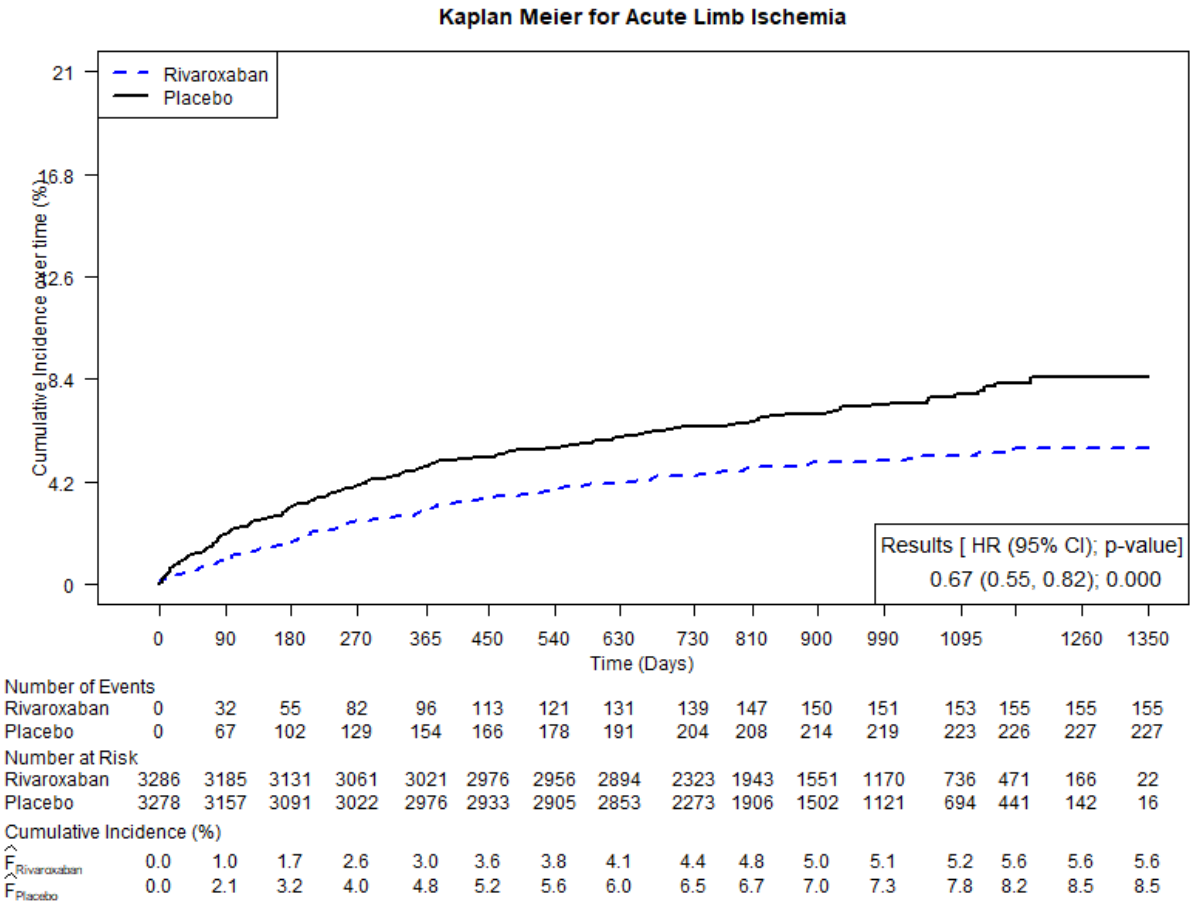
Figure 11 Kaplan Meier Curve for Time to Myocardial Infarction



Number of Events																
Rivaroxaban	0	26	40	56	68	76	89	97	102	110	116	119	123	127	131	131
Placebo	0	27	46	59	73	85	96	105	124	128	135	139	143	144	148	148
Number at Risk																
Rivaroxaban	3286	3197	3155	3101	3065	3033	3008	2949	2374	1988	1582	1189	747	472	161	20
Placebo	3278	3198	3151	3093	3058	3018	2993	2940	2355	1988	1572	1182	745	480	164	21
Cumulative Incidence (%)																
$\hat{F}_{Rivaroxaban}$	0.0	0.8	1.2	1.7	2.1	2.4	2.8	3.1	3.2	3.6	3.9	4.1	4.5	5.2	6.3	6.3
$\hat{F}_{Placebo}$	0.0	0.8	1.4	1.8	2.3	2.7	3.0	3.3	4.0	4.2	4.6	4.8	5.2	5.4	6.8	6.8

Abbreviations: HR=hazard ratio; CI=confidence interval
Source: Statistical Reviewer

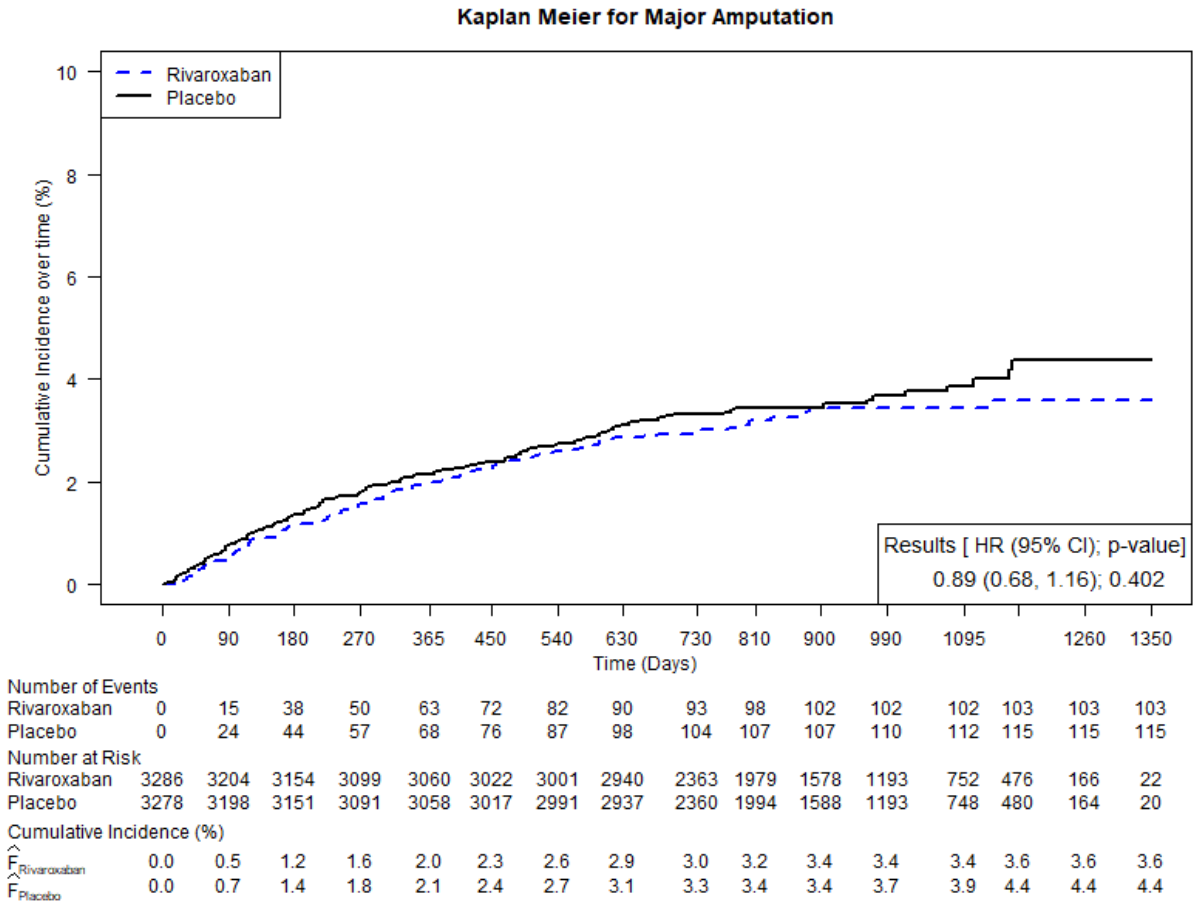
Figure 12 Kaplan Meier Curve for Time to Acute Limb Ischemia



Number of Events																
Rivaroxaban	0	32	55	82	96	113	121	131	139	147	150	151	153	155	155	155
Placebo	0	67	102	129	154	166	178	191	204	208	214	219	223	226	227	227
Number at Risk																
Rivaroxaban	3286	3185	3131	3061	3021	2976	2956	2894	2323	1943	1551	1170	736	471	166	22
Placebo	3278	3157	3091	3022	2976	2933	2905	2853	2273	1906	1502	1121	694	441	142	16
Cumulative Incidence (%)																
$\hat{F}_{Rivaroxaban}$	0.0	1.0	1.7	2.6	3.0	3.6	3.8	4.1	4.4	4.8	5.0	5.1	5.2	5.6	5.6	5.6
$\hat{F}_{Placebo}$	0.0	2.1	3.2	4.0	4.8	5.2	5.6	6.0	6.5	6.7	7.0	7.3	7.8	8.2	8.5	8.5

Abbreviations: HR=hazard ratio; CI=confidence interval
Source: Statistical Reviewer

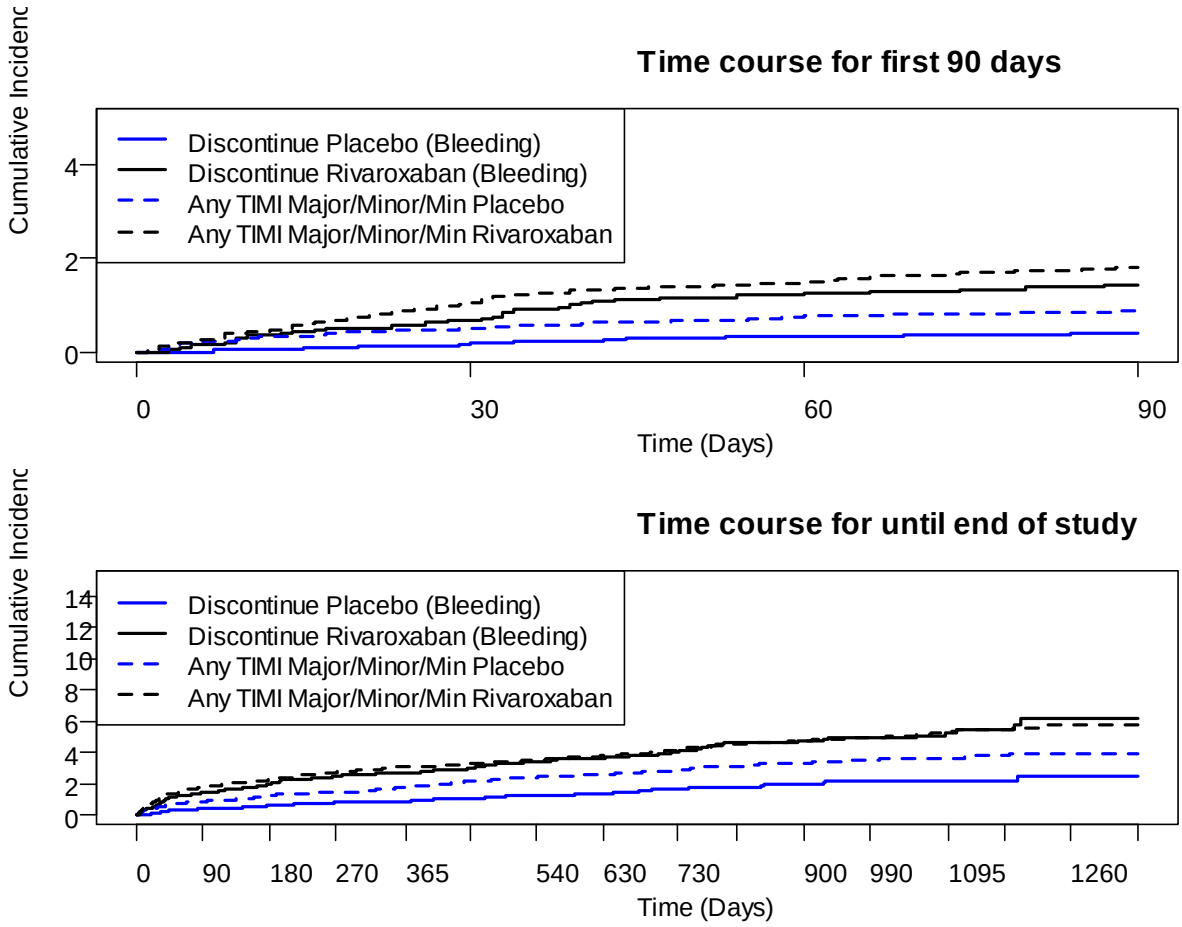
Figure 13 Kaplan Meier Curve for Time to Major Amputation of a Vascular Etiology



Number of Events																
Rivaroxaban	0	15	38	50	63	72	82	90	93	98	102	102	102	103	103	103
Placebo	0	24	44	57	68	76	87	98	104	107	107	110	112	115	115	115
Number at Risk																
Rivaroxaban	3286	3204	3154	3099	3060	3022	3001	2940	2363	1979	1578	1193	752	476	166	22
Placebo	3278	3198	3151	3091	3058	3017	2991	2937	2360	1994	1588	1193	748	480	164	20
Cumulative Incidence (%)																
$\hat{F}_{Rivaroxaban}$	0.0	0.5	1.2	1.6	2.0	2.3	2.6	2.9	3.0	3.2	3.4	3.4	3.4	3.6	3.6	3.6
$\hat{F}_{Placebo}$	0.0	0.7	1.4	1.8	2.1	2.4	2.7	3.1	3.3	3.4	3.4	3.7	3.9	4.4	4.4	4.4

Abbreviations: HR=hazard ratio; CI=confidence interval
Source: Statistical Reviewer

Figure 14 Time Course of the bleeding During the Study for the TIMI Endpoints



Abbreviations: TIMI=Thrombolysis In Myocardial Infarction (study group)
Source: Statistical Reviewer

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/s/

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NORMAN L STOCKBRIDGE
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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Decision Support and Analysis Memorandum

Date:	July 30, 2021
Goal Date:	August 23, 2021
Reviewer(s):	Leila Lackey, MHS, DEnv, Decision Support and Analysis Staff, OPSA Bethany Rue, MSc, Resource Capacity Planning Staff, OPSA
Team Leader:	Sara Eggers, PhD, Decision Support and Analysis Staff, OPSA
Drug Name:	Xarelto (rivaroxaban)
NDA/BLA #:	NDA 202439, Supplement 35
Review:	Standard
Proposed indication:	XARELTO, in combination with aspirin, is indicated to reduce the risk of major thrombotic vascular events (myocardial infarction, ischemic stroke, acute limb ischemia, and major amputation of a vascular etiology) in patients who have recently undergone a lower extremity revascularization procedure due to symptomatic PAD.
Applicant:	Janssen and Bayer

I. Executive Summary

The Division of Cardiology and Nephrology identified rivaroxaban for symptomatic peripheral artery disease as a candidate for an exploratory formal benefit-risk assessment and invited the Decision Support and Analysis Staff (DSAS) to lead this analysis. This Application was selected because of the availability of a large, well-conducted clinical trial with clinically well-defined outcomes of interest. After deciding the undertake this analysis, the review team informed the Applicant of the planned analysis in the 74-day letter and encouraged them to consider submitting their own formal benefit-risk analyses.

The Division did not believe *a priori* that this would be a challenging approval decision but did believe that the results of the quantitative benefit-risk assessment could provide unique insights into various aspects of this Application's benefit-risk assessment (e.g., temporal aspects of benefit-risk) and that building experience with the process of conducting quantitative assessment will be useful for subsequent, potentially more challenging approval decisions.

This review compares and assesses the process and results from six quantitative-benefit risk methodologies: multi-criteria decision analysis (MCDA), weighted net clinical benefit wNCB, global rank, win ratio, ordinal desirability of outcomes ranking (ordinal DOOR), and weighted desirability of outcomes ranking (weighted DOOR). Numeric weights and ordinal ranking of outcomes are derived from expert judgement and a literature review of health-state utility values. In addition to findings for the specific case of rivaroxaban for PAD, we include suggestions for further method development and testing.

The MCDA, conducted by DSAS and utilizing weights derived from the expert judgment of FDA reviewers, shows that based strictly on the results of the VOYAGER PAD trial and the tradeoffs

provided by the FDA respondents, the benefit-risk assessment does not clearly favor rivaroxaban over placebo. However, that result is sensitive to the stated tradeoff and to beliefs about the true effect of rivaroxaban on all-cause mortality. Although the VOYAGER PAD trial had an imbalance in death in favor of placebo, the opposite trend was seen in the COMPASS trial and in other large trials of rivaroxaban. When all-cause mortality rates for rivaroxaban and placebo are made consistent with the direction and magnitude of effect observed in the COMPASS trial, the MCDA model favors rivaroxaban.

The additional analyses — wNCB, global rank, win ratio, ordinal DOOR, and weighted DOOR — conducted by the Applicant and utilizing expert weights and weights identified in literature all conclude that the benefit-risk assessment favors rivaroxaban. These results are robust to the hierarchies, weights, methods, or data used but in most cases are not statistically significant. Use of the Applicant's numeric weights in DSAS's MCDA (and vice-versa) shows that the difference in conclusions may be driven by differences in weights and not by differences in methodologies.

Side-by-side comparison of the methods shows some strengths and limitations of each method. It is unlikely that there will ever be a single quantitative benefit-risk method appropriate for all contexts. Further evaluation of these methods in additional contexts is warranted to better understand the appropriate context and to increase CDER understanding of how these methods can inform regulatory decision-making.

Table of Contents

II. Introduction

a. Motivation and objectives

The Division of Cardiology and Nephrology (DCN) identified the supplemental new drug application (sNDA) for rivaroxaban for symptomatic peripheral artery disease (PAD) as potentially appropriate for an exploratory formal benefit-risk assessment of rivaroxaban for symptomatic PAD. DCN requested support from the Decision Support and Analysis Staff (DSAS) in conducting this analysis. DSAS and DCN also informed the Applicant of plans to conduct this analysis as part of the 74-day letter and encouraged the Applicant to conduct and submit their own analyses.

DCN did not *a priori* believe that the approval decision for rivaroxaban for PAD was a narrow benefit-risk, although they noted a numerical imbalance in all-cause mortality in favor of placebo.

The formal benefit-risk analyses presented here have two objectives:

1. To compare the use and performance of different quantitative benefit-risk assessment methodologies.
2. To inform the regulatory benefit-risk assessment of rivaroxaban for PAD and to explore the sensitivity of the benefit-risk balance to different assumptions about the tradeoffs between outcomes, changes in the incidence of outcomes over time, and statistical uncertainty in the incidence of outcomes.

DCN and DSAS believe that the experience gained can be useful to future situations where the benefit-risk balance may be more challenging.

b. MPPRC summary

DSAS and DCN brought the benefit-risk assessment of rivaroxaban for PAD to the Medical Policy and Program Review Council (MPPRC) twice: first to obtain input on the planned analysis, and second to obtain input on the interpretation of results for informing the regulatory benefit-risk assessment and decision. Official meeting minutes are available for both. The Council supported the Division and DSAS in these exploratory benefit-risk analyses and use of rivaroxaban as a test-case for examining the methodologies. The Council agreed that the approaches could be strengthened by planning early, applying prospectively when possible, and incorporating patient perspective. They also endorsed communication of the results with appropriate context for the likely audience.

c. Therapeutic context and regulatory background

DSAS refers the reader to the clinical and statistical review by Drs. Stockbridge and Koh for discussion of the therapeutic context and regulatory background for rivaroxaban. In brief, PAD is relatively common in US adults over 55 and is associated with significant complications, including limb-threatening ischemia and cardiovascular events, and increased risks of death. Management is challenging and additional pharmacologic therapies with evidence of safety and efficacy are needed.

Rivaroxaban was first approved in 2011 “to reduce risk of stroke and systemic embolism in nonvalvular atrial fibrillation”. Several additional indications have subsequently been approved including: “to reduce the risk of major cardiovascular events in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD).” The current sNDA differs from the prior CAD/PAD indication in two respects. First, current sNDA is for prevention of PAD-specific

outcomes, acute limb ischemia and major amputation of vascular etiology, in addition of preventions of major cardiovascular events. Second, the pivotal trial for the current sNDA enrolled PAD patients who had recently (within the past week) had a revascularization procedure; as a result, the patients may have more advanced or severe PAD than the PAD patients in the pivotal trial supporting the prior approval.

d. Methods

Formal benefit-risk analyses may add value for cases involving tradeoffs between the drug's expected benefit and risks. Several analytical approaches are available to integrate benefit and risk information with information about relative desirability and tradeoffs. These are frequently referred to as "quantitative benefit-risk assessment" methodologies.

Quantitative benefit-risk assessment employs modeling techniques to allow us to transparently and explicitly assess an important decision factor: how judgements about relative importance affect the benefit-risk balance. Like all models, they are a simplification of reality and have limitations that should be recognized and considered. Nevertheless, often the process and results can be useful for identifying and testing judgements and assumptions.

Quantitative benefit-risk assessment is limited to factors amenable to quantification, such as health outcomes and states. Other aspects that necessarily factor into regulatory decisions, such as regulatory precedent or untested risk mitigation measures, cannot be readily included. While quantitative benefit-risk analyses cannot completely replace the decision-making process or account for all decision factors, the process and results can inform regulatory assessment by offering a platform for identifying assumptions and judgements and a mechanism for comparing options.

We also acknowledge that the weights proposed for use here are grounded in subjective judgements. However, these subjective judgements are at play in all decisions. Quantitative benefit-risk assessment methods provide an approach for externalizing these judgements, identifying when individuals may hold different judgements, and testing their impact on the decision.

The methods utilized here can be "classified" based on key characteristics. First, is whether the analyses are performed based on group-level incidence rates (MCDA and wNCB) or is integrated at the individual patient level (global rank, win ratio, ordinal DOOR, and weighted DOOR). Second is whether the analysis incorporates numeric weights for the relative desirability of outcomes (MCDA, wNCB, and weighted DOOR) or ordinal ranking of outcome desirability (global rank, win ratio, and ordinal DOOR). Third is whether the methodology combines different outcomes into "benefit-risk composites" (ordinal DOOR and weighted DOOR) or does not form these composites (MCDA, wNCB, global rank, and win ratio). Table 1 summarizes, in the opinion of DSAS, the most relevant strengths and limitations of the methods. The next sections present each of these methods in turn.

Table 1. Quantitative benefit-risk assessment methods used.

Method	Description	Key Strength	Key Limitation
Group-level analysis using numeric weights and no benefit-risk composite outcomes			
MCDA[A]	"Final grade" based on the sum product of performance and importance	Builds on typical approach to benefit-risk assessment; flexible for any data type	Weighting process is challenging; numerical result has no obvious interpretation
wNCB[B]	Overall difference in risk of "death equivalents"	Numerical results are potentially easier to interpret than MCDA	Requires binomial outcomes
Patient-level analysis using ordinal desirability and no benefit-risk composite outcomes			
Global Rank[B]	Rank participants based on the "worst" outcome experienced	Intuitive ranking based on event severity and time to event	Difference between adjacent outcomes is equal; only considers one outcome per participant
Win Ratio[B]	Compare each possible pair of participants to determine the ratio of wins to losses	Intuitive comparisons based on event severity and time to event	All wins and losses have equal importance; only considers one outcome per participant
Patient-level analysis using ordinal desirability and benefit-risk composite outcomes			
Ordinal DOOR[B]	Rank participant based on their overall outcome	Intuitive ranking based on overall outcome; simultaneously considers multiple events for a participant	Outcome categories are heterogenous; difference between adjacent categories is equal
Patient-level analysis using numeric weights and benefit-risk composite outcomes			
Weighted DOOR[B]	Score each participant based on their overall outcome	Weighting accounts for unequal differences between adjacent categories; simultaneously considers multiple events for a participant	Outcome categories can be heterogeneous, making weighting more cognitively challenging

[A] Applied by DSAS
[B] Applied by the Applicant

III. Multi-Criteria Decision Analysis

MCDA (Thokala, 2016; Marsh, 2016) mathematically combines information on multiple criteria (in the pharmaceutical benefit-risk assessment context, the desired and undesired clinical outcomes of a treatment option), into a single score between 0 (worst) and 1 (best). Comparing scores between treatment options (called "alternatives" in MCDA), in this case rivaroxaban 2.5 mg + ASA 100 mg and placebo + ASA 100 mg, can provide information about which is preferable and the sensitivity of that conclusion to uncertainty in incidence rates and weights.

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force on emerging good practices for MCDA defines eight steps for MCDA (Thokala 2016):

1. Defining the decision problem: identify objectives, type of decision, alternatives, stakeholders, and output required
2. Selecting and structuring criteria: identify criteria relevant for evaluating alternatives
3. Measuring performance: gather data about the alternatives performance on the criteria and summarize this in a "performance matrix"
4. Scoring alternatives: elicit stakeholders' preferences for changes within criteria
5. Weighting criteria: elicit stakeholders' preferences between criteria

6. Calculating aggregated scores: use the alternatives' scores on the criteria and the weights for the criteria to get "total value" by which the alternatives are ranked
7. Dealing with uncertainty: perform uncertainty analysis to understand the level of robustness of the MCDA results
8. Reporting and examination of findings: interpret the MCDA outputs, including uncertainty analysis, to support decision making

a. Step 1: Defining the decision problem

The objective of this MCDA is to assess the sensitivity of the benefit-risk balance of rivaroxaban for symptomatic PAD to different tradeoffs between outcomes and to determine if the benefit-risk balance changes over time. The regulatory decision informed by the analysis is the approval decision for the supplemental NDA. "Alternatives" (treatment options) are defined as rivaroxaban 2.5 mg + ASA 100 mg (referred to simply as rivaroxaban) and placebo + ASA 100 mg (referred to simply as placebo). Stakeholders to the decision and the analysis are both internal (other review Divisions and offices) and external (sponsors, physicians, and patients).

b. Step 2: Selecting and structuring criteria

Criteria for this MCDA, referred to as "outcomes" here, are based on the primary efficacy endpoint and principal safety endpoints for VOYAGER PAD with a few additions (Table 2). For reference, the primary efficacy endpoint was the composite of first cardiovascular death, ischemic stroke, myocardial infarction, acute limb ischemia, and major amputation of a vascular etiology; the principal safety endpoint was first TIMI major bleed, which can be subset into first fatal bleed, non-fatal intracranial bleed, and other non-fatal bleeds Starting from this set of outcomes, the review team made the following modifications:

- Replacement of the two fatal outcomes with a single measure of mortality: all-cause mortality.
- Addition of prevention of the need for revascularization procedures after randomization. The proposed indication is for patients with PAD soon after a revascularization procedure.
- Addition of other bleeding events (TIMI minor bleeds, TIMI bleeds requiring medical attention, and TIMI minimal bleeds) as undesired outcomes. While generally not as clinically significant, patients view any bleeding event as undesirable.

To avoid double counting, all outcomes besides all-cause mortality are limited to non-fatal[1] events (the subject was alive for at least 30 days following the event). We note that the division between benefits and risks is potentially misleading as all events are undesirable. Trial protocol definitions were used for the outcomes in the FDA value tree.

[1] Here and throughout, non-fatal was defined as an event occurring more than 30 days before death.

Table 2. FDA Value Tree (all are first-events).

Rivaroxaban for Symptomatic PAD	Benefits or desired outcomes (*reduced risk of events)*	• All-cause mortality • Non-fatal ischemic stroke • Non-fatal myocardial infarction • Non-fatal acute limb ischemia • Non-fatal major amputation of vascular etiology • Need for revascularization procedure after randomization
	Risks or undesired outcomes (*increased risk of events)*	• Non-fatal TIMI intracranial bleed • Non-fatal, non-intracranial TIMI major bleed • Non-fatal TIMI minor bleed • Non-fatal TIMI bleed requiring medical attention • Non-fatal TIMI minimal bleed

c. Step 3: Measuring performance

Performance of the two treatment options (rivaroxaban and placebo) was assessed using the results of the VOYAGER PAD trial (ADaM dataset included in Seq 0425; May 7, 2021). Figure 1 provides the risk difference over time from the VOYAGER PAD trial for the clinical outcomes specified in the FDA value tree at 6-month intervals. As expected, the risk difference for non-fatal bleeding events is positive, indicating an increased risk of bleeding from rivaroxaban vs placebo, while the risk difference for non-fatal, non-bleeding events is below zero, indicating a benefit of rivaroxaban over placebo. Notably, there is a trend towards higher risk of all-cause mortality in the rivaroxaban arm vs placebo at all time points. Table 3 provides the number at risk for each timepoint and event type. Small numbers of patients at risk at 42 and 48 months (Table 3), make these estimates less reliable and informative.

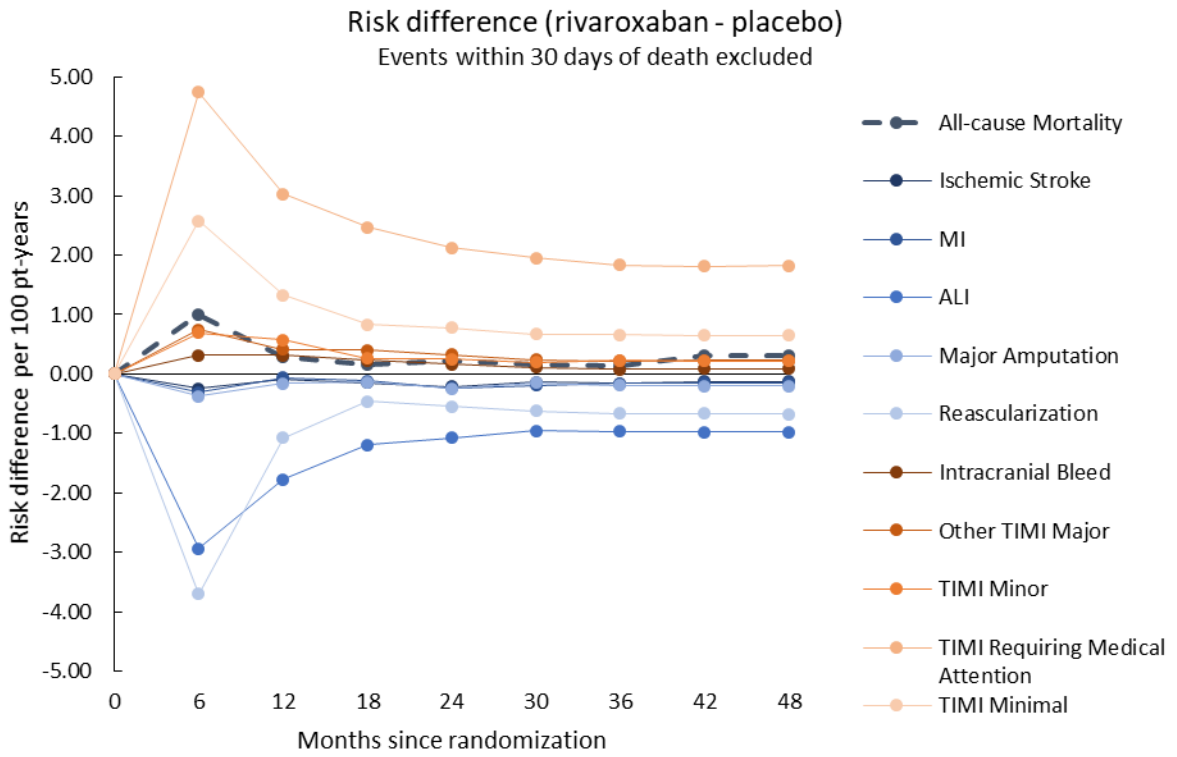

Figure 1. Risk difference over time. Values above 0 indicate the event was more common in the rivaroxaban arm. Small numbers of patients at risk at 42 and 48 months (Table 3), make these estimates less reliable and informative.

Table 3. Subjects at risk. With exception of all-cause mortality, events within 30 days of death are excluded.

		Months since randomization								
Outcome	Treatment	0	6	12	18	24	30	36	42	48
All-cause mortality	Rivaroxaban	3286	3214	3158	3100	2460	1587	789	124	
	Placebo	3278	3221	3155	3097	2469	1588	786	124	1
Ischemic stroke	Rivaroxaban	3286	3171	3081	3022	2390	1526	757	116	
	Placebo	3278	3166	3082	3012	2382	1530	753	118	1
MI	Rivaroxaban	3286	3151	3057	2999	2371	1507	744	115	
	Placebo	3278	3145	3053	2985	2351	1498	739	113	1
ALI	Rivaroxaban	3286	3128	3016	2946	2321	1478	734	118	
	Placebo	3278	3084	2976	2900	2271	1432	688	93	1
Major amputation	Rivaroxaban	3286	3151	3054	2995	2362	1506	749	117	
	Placebo	3278	3147	3058	2988	2358	1512	742	111	1
Revascularization	Rivaroxaban	3286	2848	2550	2370	1765	1078	507	80	
	Placebo	3278	2798	2533	2368	1770	1076	491	63	1
Intracranial bleed	Rivaroxaban	3286	3176	3098	3049	2416	1545	767	120	
	Placebo	3278	3180	3108	3051	2416	1548	762	117	1
Other TIMI major	Rivaroxaban	3286	3166	3086	3031	2398	1537	763	118	
	Placebo	3278	3177	3102	3044	2411	1544	762	119	1
TIMI minor	Rivaroxaban	3286	3157	3071	3019	2380	1518	754	115	
	Placebo	3278	3169	3095	3029	2394	1531	753	118	1
TIMI requiring	Rivaroxaban	3286	3019	2896	2802	2188	1392	682	107	
medical attention	Placebo	3278	3088	2986	2903	2272	1448	700	104	1
TIMI minimal	Rivaroxaban	3286	3086	2995	2941	2308	1478	725	117	
	Placebo	3278	3127	3037	2971	2345	1505	740	112	1

Of note in Figure 1 is the imbalance in all-cause mortality in favor of placebo. The review team's judgement at the start of the MCDA process was that this adverse trend was not a plausible finding. Two prior trials for rivaroxaban, ATLAS-ACS and COMPASS showed all-cause mortality and CV death to be less frequent in rivaroxaban-treated patients compared to placebo-treated:

- ATLAS-ACS: patients with recent acute coronary syndrome (ACS); N = 14,473
    - All-cause mortality: 2.58 per 100 patient-years in rivaroxaban-treated patients and 3.04 in placebo-treated; hazard ratio 0.85 (95% CI 0.71, 1.02)
- COMPASS: patients with CAD or PAD; N = 18,278
    - All-cause mortality: 3.4 per 100 patient-years in rivaroxaban-treated patients and 4.1 in placebo-treated; hazard ratio 0.82 (95% CI 0.71-0.96)
    - CV death: 1.7 per 100 patient-years in rivaroxaban-treated patients and 2.2 in placebo-treated; hazard ratio 0.78 (95% confidence interval 0.64-0.96)

d. Step 4: Scoring alternatives

Scoring is a three-step process. First, the best and worst plausible values for each outcome are defined. Commonly, and in the absence of other information, the best and worst are defined in order to encompass the 95% confidence intervals of the performance of each treatment option. Therefore, the best-worst range was calculated for each outcome and timepoint based on the lower-lower bound and the upper-upper bound of the rivaroxaban and placebo arms.

Second, we determine the incremental importance of changes between the best and worst plausible values. As all outcomes in Table 2 represent individuals experiencing an event, changes within outcomes were defined using a linear function. In other words, each additional person experiencing their first event is equally important. Non-linear functions are more frequently used for categorical outcomes (such as the value of different categories on a patient-reported outcome) or for continuous outcomes, such as biomarkers, where changes may have different significance depending on the starting value (for example, reducing HbA1c from 10 to 9 versus reducing HbA1c from 6 to 5).

Third, we used the assumed linear function to normalize the performance of the treatment option from 0 to 1 using the worst plausible (set to 1) and worst-plausible (set to 1) values.

e. Step 5: Weighting criteria

Weights for each outcome were calculated from tradeoffs (Table 4) against all-cause mortality provided by five individuals involved with the rivaroxaban sNDA for symptomatic PAD (three with a clinical background — A, D, and E — and two with a statistical background — B and C) and two FDA cardiologists not familiar with the application (F and G). We acknowledge that robust information about the tradeoffs patients would be willing to make would be desirable. However, this information is not available for this context and set of outcomes.

For FDA respondents, the tradeoffs (Table 4) were all made against all-cause mortality, corresponding to the following questions (ischemic stroke as an example; the answer to both questions should be the same):

- How many more patients would have to avoid an ischemic stroke to have the same benefit of preventing one death?
- How many patients with ischemic strokes are equivalent to one death?

When considering the tradeoff questions, the respondents were provided with the definition of each event as well as supplemental information about:

- available baseline characteristics for the subjects experiencing the event that might indicate the severity of the event (Appendix Table A1),
- available event characteristics indicative of the severity of the event (Appendix Table A2), and
- patient responses to the visual analog scale component of the EuroQol 5-dimension, 5-level (EQ-5D-5L) questionnaire (Appendix Figure A1).

Table 4. Tradeoffs against all-cause mortality. Tradeoffs were provided by each respondent as an individual response and a plausible range.

	Respondents familiar with sNDA					Other FDA	
Outcome	A	B	C	D	E	F	G
Ischemic stroke	1	3	7	5	3	5	5
	0.5-2	2-5	3-15	1-30	2-4	5-7	3-20
Myocardial infarction	5	3	4	5	4	8	8
	2-10	2-4	2.5-7.5	2-30	3-5	7-10	5-20
Acute limb ischemia	20	5	15	20	6	5	7
	5-20	3-10	10-20	5-50	5-7	5-7	3-15
Major amputation of	10	2	7.5	20	5	8	5
vascular etiology	2-10	2-3	5-15	5-50	4-6	7-10	2-20
Revascularization	40	5	25	75	9	9	15
procedure	5-50	3-10	20-40	50-200	8-12	8-9	12-40
TIMI intracranial bleed	1	1	8	2	2	4	5
	0.5-2	1-1	10-20	1-10	2-3	4-6	2-10
Non-intracranial TIMI	40	10	15	30	7	7	7
major bleed	540	5-20	10-25	20-100	6-9	6-7	3-15
TIMI minor bleed	50	365	75	100	25	8	15
	5-50	180-∞	50-100	50-300	20-40	7-10	10-40
TIMI bleed requiring	100	365	125	300	9	8	30
medical attention	5-50	180-∞	100-150	100-500	8-20	7-10	20-50
TIMI minimal bleed	∞	∞	150	500	35	10	∞
	10-∞	∞-∞	100-200	300-1000	30-70	9-10	∞-∞

Lower tradeoffs in Table 4 indicate that the outcome is less desirable (for example, for review team member A, ischemic strokes are considered less desirable than myocardial infarctions). Tradeoffs less than 1 indicate that the outcome is less desirable than death. An infinite tradeoff (∞) was treated mathematically with a weight of zero.

Tradeoffs were heterogeneous but generally indicate the respondents place the greatest weight on ischemic stroke and intracranial bleeds, followed by myocardial infarction. Respondents also generally place more weight on acute limb ischemia, major amputations, and revascularization procedures than they do on non-fatal, non-intracranial bleeds.

f. Step 6: Calculating aggregated scores

The basic MCDA score calculation (Appendix Table A3) is the sum product of individual performance (Figure 1) and importance weights (derived from the weights in Table 4). Comparing the difference in MCDA scores can indicate if an alternative, rivaroxaban or placebo, is preferred given the observed performance and the stated weights. Figure 2 provides the results of the MCDA calculation as the difference in total MCDA scores (rivaroxaban – placebo)

over time. The graph plots the results for each respondent, A-G. Differences above zero indicate a preference for rivaroxaban given the tradeoffs in Table 4 and the incidence rates from the VOYAGER PAD trial. For all respondents a maximum occurs at 36 months. With the exception of respondent B, total MCDA score differences tend to favor placebo although the differences are generally small (-0.1 to 0.1) relative to the potential range for MCDA (-1 to 1). Clear "rules" for a meaningful score difference are not available.

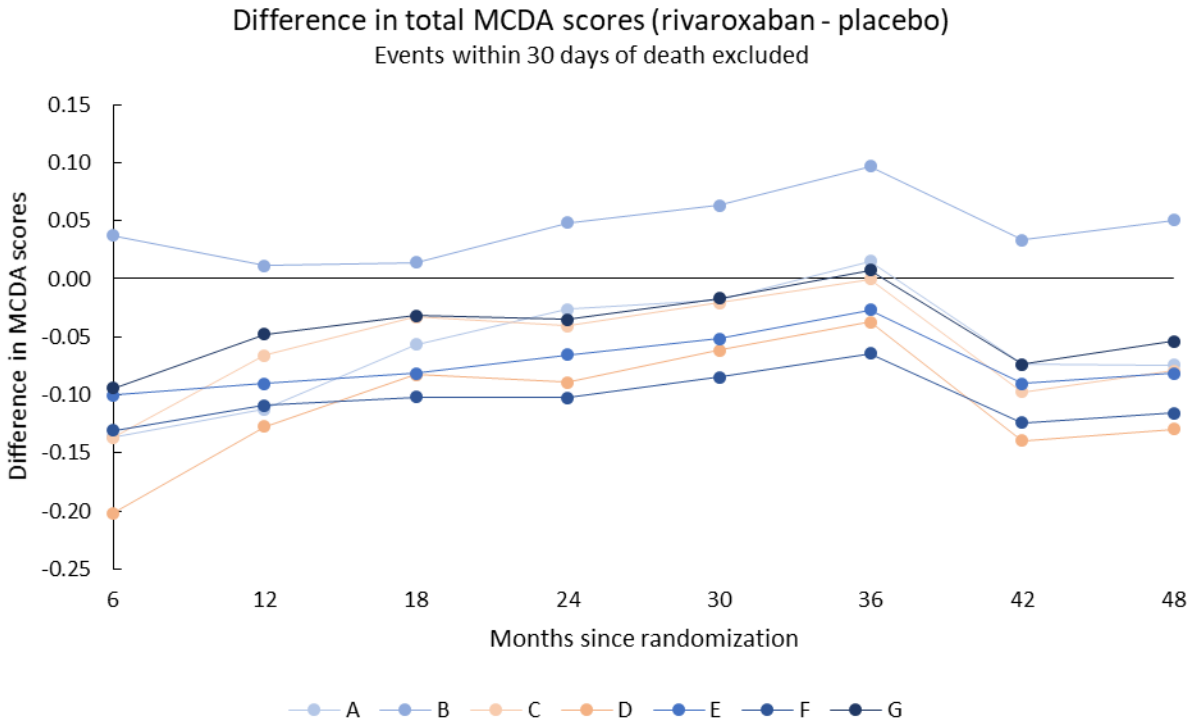

Figure 2. Difference in total MCDA scores. Values above 0 indicate a preference for rivaroxaban given the specified tradeoffs and incidence rates observed in the VOYAGER PAD trial. Small numbers of patients at risk at 42 and 48 months (Table 3), make these estimates less reliable and informative.

Total MCDA scores are the sum of outcome-level scores. Considering the outcome-level MCDA scores can identify which outcome is driving differences between the two alternatives. Figure 3 provides outcome-level MCDA score differences between rivaroxaban and placebo. As with the total MCDA scores, a difference above 0 indicates that rivaroxaban is preferred over placebo for that outcome. The "most-positive" score differences correspond to the outcomes that are driving the positive value of rivaroxaban over placebo and the "most-negative" score differences are the ones driving the negative value of rivaroxaban compared to placebo.

Based on the tradeoffs specified in Table 4 and the incidence rates observed in the VOYAGER PAD trial, all-cause mortality is the largest contributor to the negative value of rivaroxaban compared to placebo (Figure 3A), followed by TIMI bleeds requiring medical attention (Figure 3J) and intracranial bleeds (Figure 3G). Acute limb ischemia (Figure 3D), revascularization procedures (Figure 3F), and major amputation of vascular etiology (Figure 3E) are the largest positive values for rivaroxaban over placebo. Ischemic stroke was also a substantial contributor to the positive value of rivaroxaban for respondent B (Figure 3B).

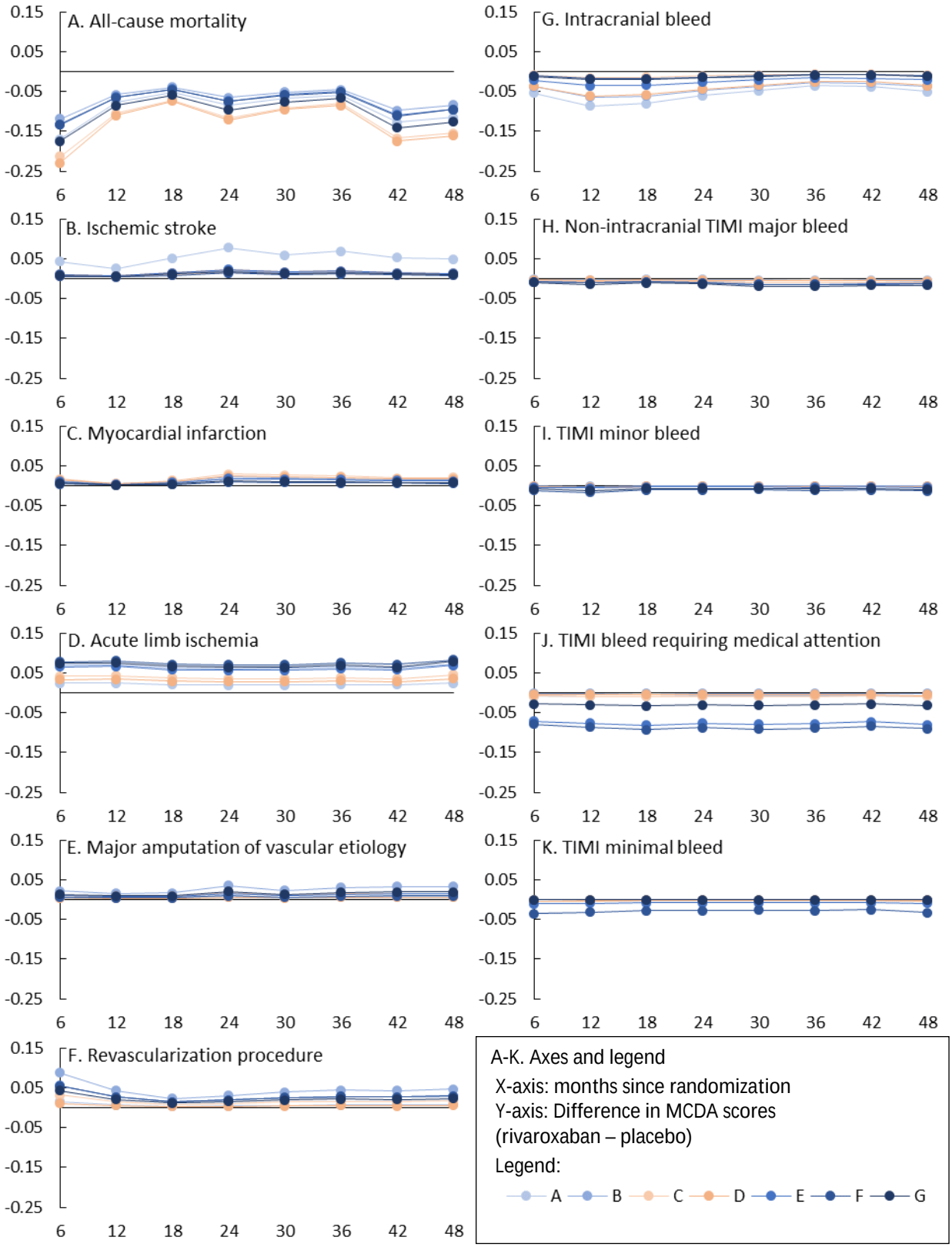

Figure 3. MCDA score differences by outcome. Values above zero indicate the performance of rivaroxaban exceeds placebo. Small numbers of patients at risk at 42 and 48 months (Table 3), make these estimates less reliable and informative.

g. Step 7: Dealing with uncertainty

Uncertainty in MCDA results can come from several sources, applies principally to the weights and incidence rates used, and can be due to variability in observed values (i.e., statistical uncertainty and heterogeneity) and systematic differences between the sample we have observations for and the population of interest (i.e., known and unknown biases and confounders). To evaluate the sensitivity of the results to statistical uncertainty and heterogeneity, we conducted a one-way sensitivity analysis of weights and a multi-way sensitivity analysis of weights and incidence rates. We also considered systematic uncertainty in all-cause mortality incidence by conducting a scenario test using the results of the COMPASS trial.

First, we conducted a one-way sensitivity analysis to evaluate the sensitivity of the result to variability in the tradeoffs. We varied the weights by considering the overall minimum and maximum tradeoffs based on the seven respondents (Table 4). In the tornado plots in Figure 4, the width of the bar represents the minimum and maximum difference in total MCDA scores (rivaroxaban – placebo) for a particular sensitivity analysis for a single tradeoff.

Results (Figure 4) show that the difference in the total MCDA scores is, for all timepoints, sensitive to tradeoffs given for acute limb ischemia and revascularization procedures against death. In other words, the more weight given to prevention of acute limb ischemia and revascularization procedures, the more favorable one would find rivaroxaban relative to placebo. After 12 months of treatment, the total MCDA score difference becomes sensitive to the tradeoffs given for additional outcomes, including ischemic stroke (12 months and later), major amputation (24, 30, and 36 months), and myocardial infarction (30 and 36 months). At 36 months, the total MCDA score difference is also sensitive to the tradeoffs given between bleeding events and death. For all types of bleeding events considered, the less weight given to bleeding events the more favorable one would find rivaroxaban relative to placebo.

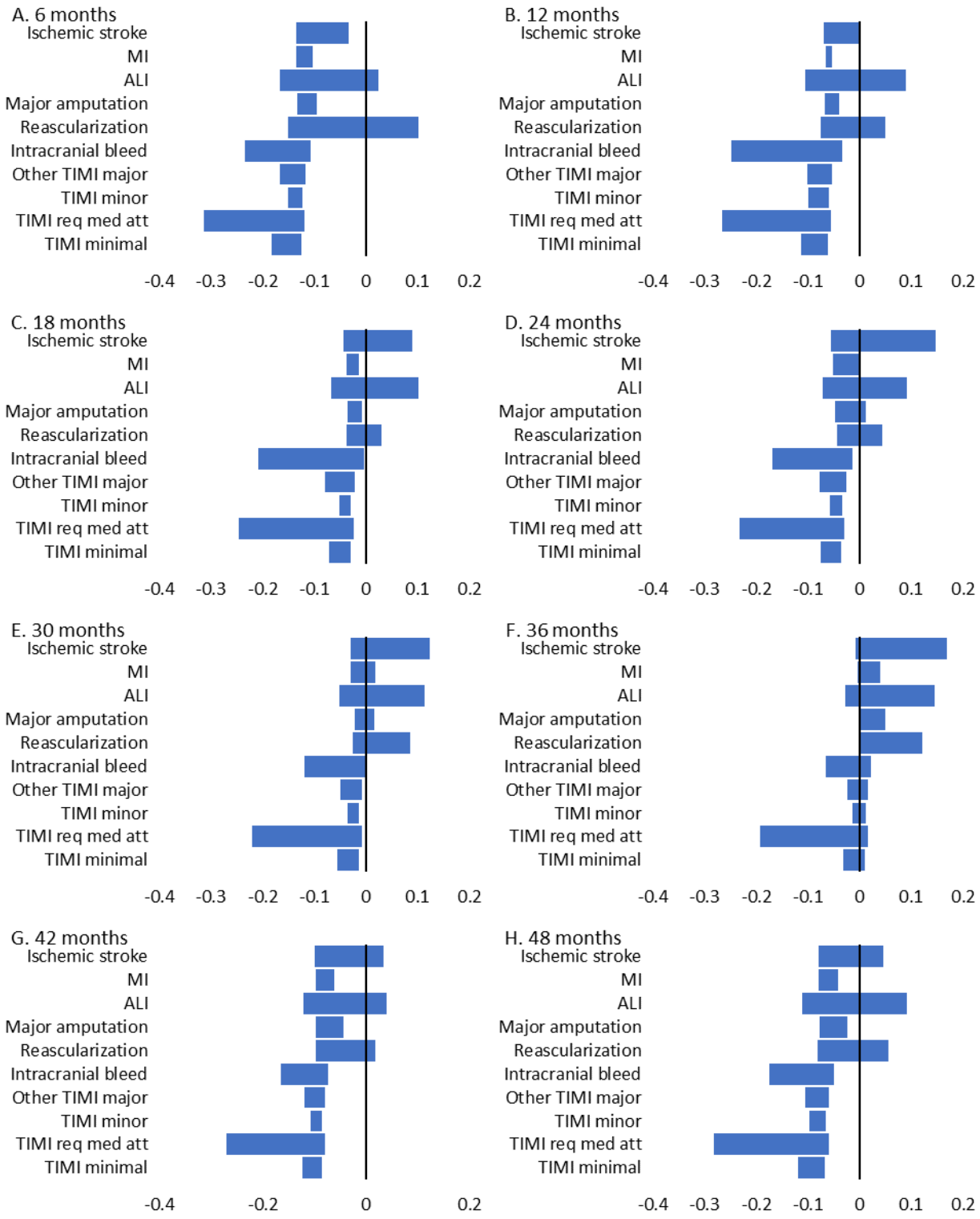

Figure 4. One-way sensitivity testing for uncertainty in weights. X-axis is the difference in total MCDA scores (rivaroxaban – placebo). Bars crossing zero indicate the total MCDA score difference is sensitive to the tradeoff between the given outcome and death. Small numbers of patients at risk after 36 months (G and H), and in particular by 48 months (Table 3), make these estimates less reliable and informative.

Second, we also considered the simultaneous uncertainty in tradeoffs and incidence rates through multi-way sensitivity testing by repeated simulation using stochastic multi-attribute acceptability analysis (SMAA) (Tervonen, 2008). This method uses repeated simulations where weights are randomly selected from a given range (derived from the plausible tradeoff range shown in Table 4). Each iteration the treatment option with a greater MCDA score is recorded. After simulations are complete, the percent of simulations where a given treatment option is preferred is reported. SMAA can also be used to test sensitivity to uncertainty in the performance estimates. In this variation, outcome performance is randomly selected from the statistical distribution of the performance estimate.

Figure 5 provides the percent of iterations where rivaroxaban was preferred over placebo. Percentages above 50 indicate rivaroxaban is more likely to be preferred over placebo and increase confidence in positive MCDA score differences found in Figure 2. Similar to Figure 2, results based on respondent B's tradeoffs are most favorable for rivaroxaban and results for all respondents reach a peak at 36 months.

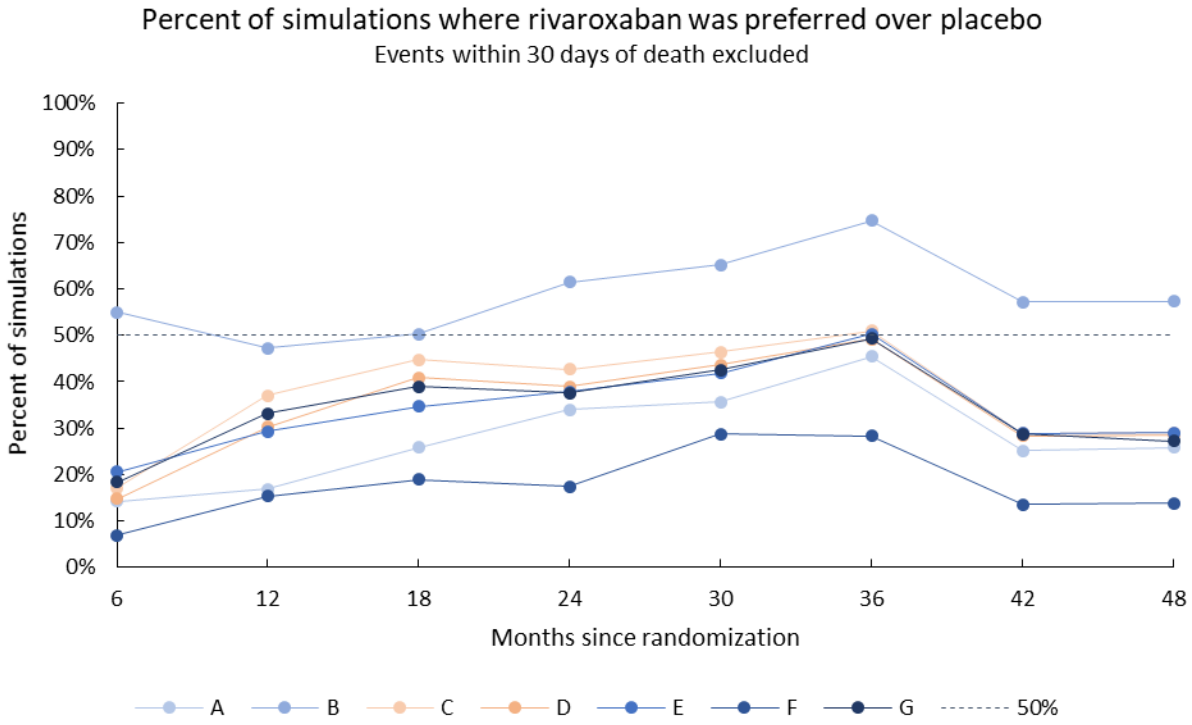

Figure 5. Multi-way sensitivity testing for uncertainty in incidence rates and weights. Individual traces shown for each FDA respondent. Percentages above 50% suggest rivaroxaban is more likely to be preferred over placebo. Small numbers of patients at risk at 42 and 48 months (Table 3), make these estimates less reliable and informative.

Third, because of the sensitivity of the MCDA results to all-cause mortality (Figure 3), and because of the pre-specified belief of the review team that the all-cause mortality imbalance in VOYAGER PAD was not a plausible finding, we conducted two scenario tests for different rates of all-cause mortality for rivaroxaban and placebo.

The first scenario test was to assume no difference in all-cause mortality between the treatment arms (Figure 6). This scenario increased the MCDA score difference for all respondents although respondent F still had a negative score difference for all timepoints.

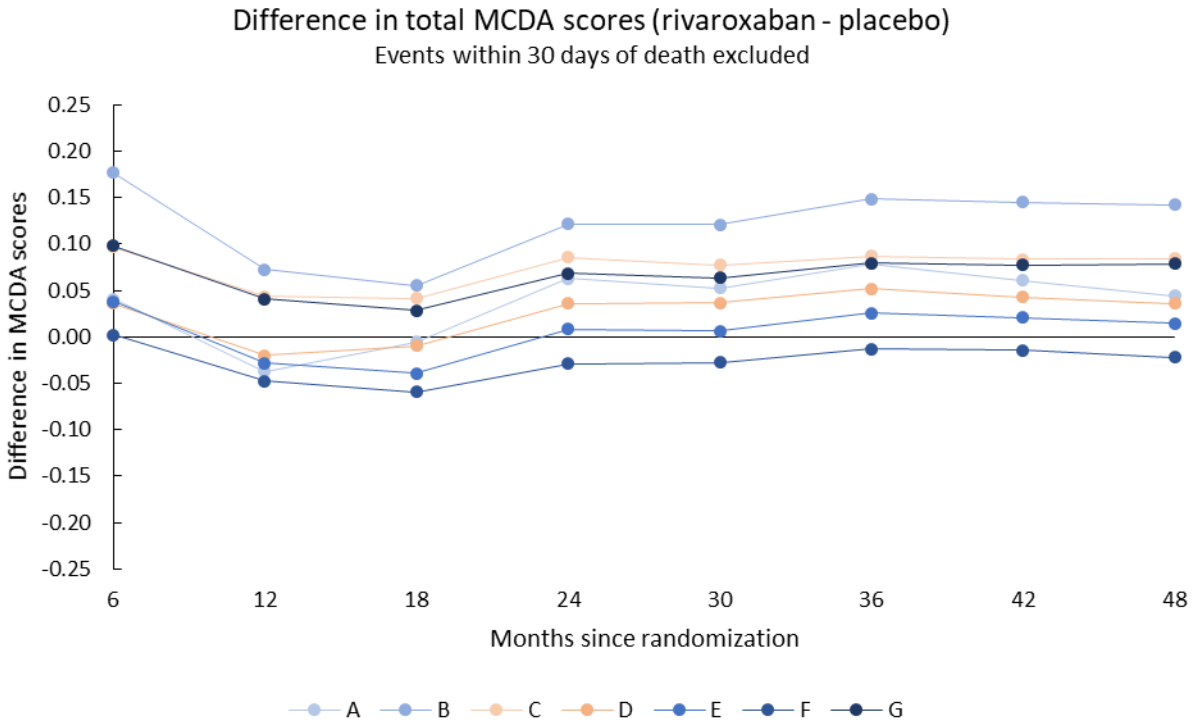

Figure 6. Difference in total MCDA scores assuming no difference in all-cause mortality between rivaroxaban and placebo.

For a second scenario test, we assumed all-cause mortality rates consistent with the results from the PAD subgroup in the COMPASS trial (Figure 7). The reasonableness of this assumption is a question of clinical judgement and there may be differences between experts in the validity of this prior information to the decision at hand. If one believes the COMPASS results are relevant, MCDA score differences for all respondents were above zero, indicating a preference for rivaroxaban over placebo. Small numbers of patients at risk at 42 and 48 months (Table 3), make these estimates less reliable and informative.

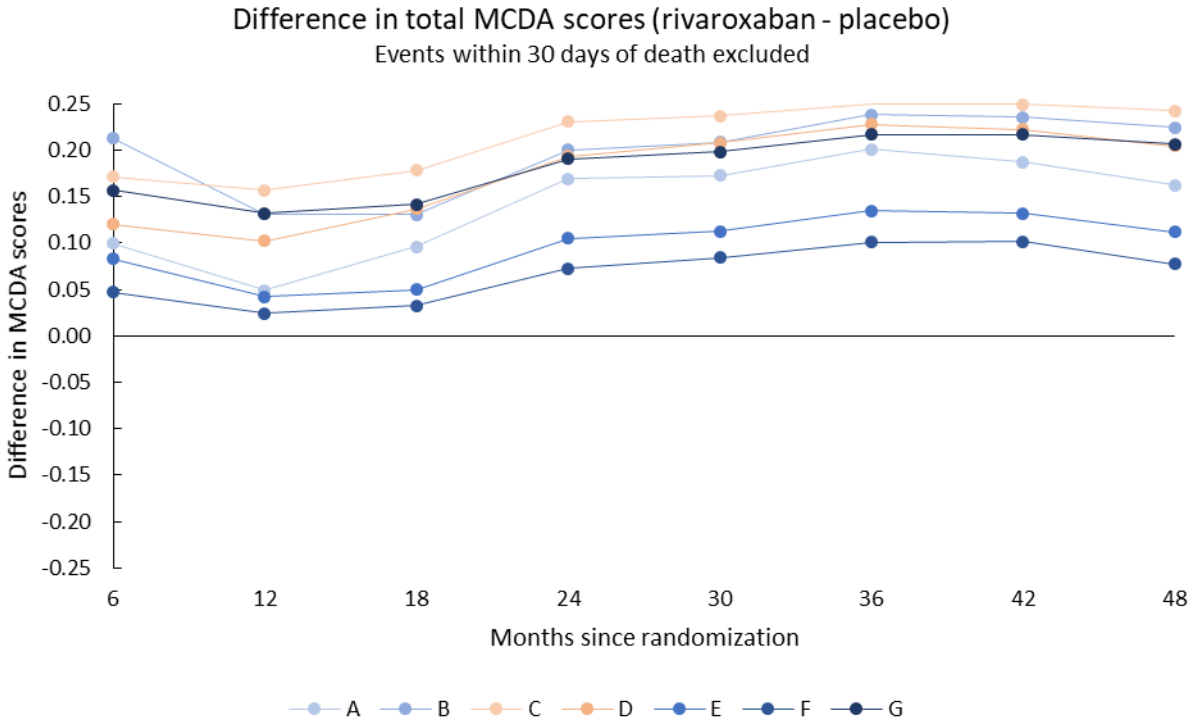

Figure 7. Difference in total MCDA scores assuming rates of all-cause mortality consistent with the PAD subgroup in the COMPASS trial. Small numbers of patients at risk at 42 and 48 months (Table 3), make these estimates less reliable and informative.

h. Step 8: Reporting and examination of findings

Results of the MCDA were presented internally to the FDA review team (which includes the decision-maker for the sNDA) and to other FDA stakeholders. This presentation fostered discussion of a range of issues including heterogeneity and variability of weights, the appropriateness of decision-making without patient weights, the plausibility of the all-cause mortality result in the VOYAGER PAD trial, and the communication of analyses externally.

i. MCDA: Method Assessment

MCDA provides a structured benefit-risk assessment methodology that builds upon the typical approach to appraising the benefits and risks of a drug. Review teams are accustomed to identifying the important benefits and risks for consideration and summarizing the available evidence. MCDA adds to this process by also specifying the relative importance or tradeoffs between outcomes, allowing for numerical exploration and sensitivity testing.

The crux of MCDA lies on specification of the weights and tradeoffs between outcomes. While specification is challenging and the resulting weights are often heterogenous between individuals, these judgements are a part of all benefit-risk assessments and decisions. The MCDA process forces the externalization of these judgements and provides a framework for the team to discuss relative importance.

IV. Weighted Net Clinical Benefit

The Applicant submitted a benefit-risk analysis closely related to, but distinct from, MCDA: weighted net clinical benefit (wNCB; see Seq 0433; May 27, 2021). In contrast to MCDA, which results in constrained utilities between 0 and 1, wNCB produces a "death-equivalents" risk difference between rivaroxaban and placebo (Nixon et al, 2016). In this approach, the risk difference between rivaroxaban and placebo is calculated for each outcome and then weighted proportional to the "cost" of each outcome relative to death. Death, the least desirable outcome, receives a weight of 1. Less-desirable or more "costly" outcomes have weights closer to 1 and more-desirable or less "costly" outcomes have weights closer to 0. wNCB requires binary outcomes; continuous or categorical variables must be converted into a responder definition in order to be used for a wNCB analysis.

Other important differences between the Agency's MCDA and the Applicant's wNCB include the outcomes used and the source of weights. Weights are discussed further in the following section. For the outcomes, the Applicant's value tree was based on the components of the pre-specified, adjudicated primary efficacy and safety endpoints[2]. The Agency's value tree is effectively an expansion of the Applicant's where the Agency also considered the less clinically significant outcomes of revascularization procedures and non-major TIMI bleeds.

a. Weights: Literature health state utility values

The Applicant conducted a systematic literature review for published health-state utility values (HSUVs) comparable to the outcomes and population in the VOYAGER PAD trial. The initial search identified 373 HSUVs. After review, 159 were selected for inclusion and averaged by outcome to produce the mean HSUVs shown in Table 5. HSUVs represent, on a scale of 0-1, the health status for an individual after experiencing an outcome. 1 indicates perfect health while 0 indicates death. Weights for the wNCB analysis are equal to 1 minus the HSUV. The values in Table 5 differ substantially from those generated by FDA respondents (Table 4). Notably, the resulting weights place more weight on major amputation, acute limb ischemia, and non-fatal, non-intracranial major bleeding than the FDA respondents, so much so that the equivalent tradeoffs in Table 5 are outside the plausible ranges of all FDA respondents for these outcomes.

[2] CV death and fatal bleeding being handled two ways: (i) as the composite of CV death and fatal bleeding and (ii) as all-cause mortality.

Table 5. Mean HSUVs and weights by outcome based on Applicant's literature review.

Outcome	Mean HSUV (SD), n[A]	Mean weight[B]	Equivalent tradeoff[C]
Death	NA	1	1
Non-fatal ischemic stroke	0.65 (0.19), n=45	0.35	2.9
Non-fatal myocardial infarction	0.78 (0.13), n=48	0.22	4.5
Non-fatal acute limb ischemia	0.64 (0.17), n=52	0.36	2.8
Non-fatal major amputation	0.41 (0.13), n=6	0.59	1.7
Non-fatal major intracranial bleeding	0.58 (0.24), n=5	0.42	2.4
Non-fatal major non-intracranial bleeding	0.78 (0.11), n=3	0.22	4.5

[A] n: number of published HSUVs included in the average
[B] Mean weight = 1 – Mean HSUV
[C] Equivalent tradeoff = 1 / Mean weight
Source: Table 25 of the br-analysis.pdf; Seq 0433; May 27, 2021

To review the mean HSUVs in Table 5, DSAS considered the recommendations of the ISPOR task force for good practices in identification, review, and use of literature HSUVs (Brazier, 2019). The ISPOR task force recommends balancing a number of considerations when identifying literature HSUVs. Principally: (i) HSUVs should be derived from the same overarching population (e.g., patients, providers, or general public); and, (ii) HSUVs should be calculated using the same measure (e.g., the EQ-5D). Additional considerations to balance include, among others, the specific population characteristics (country, health condition), outcome characteristics (definition, severity), timeframe for assessment (immediately after the event or at a later point in time), study quality and size, and age of the study.

The Applicant did not follow an approach consistent with the recommendations of the ISPOR task force. Most significantly, the Applicant averaged HSUVs from different populations (patients, providers, and the general public) and different measures (Seq 0442; June 25, 2021). Instead, the Applicant primarily relied on matching the health condition and outcome definitions from the VOYAGER PAD trial as the major considerations for identifying literature HSUVs.

Because the Applicant did not follow the Good Practices defined by ISPOR, DSAS developed an algorithm for identifying literature HSUVs that better accounts for ISPOR recommendations. This algorithm was limited to the information supplied by the Applicant for each HSUV (study population, outcome definition, sample size, etc.). The DSAS-proposed algorithm is as follows:

1. Include: HSUVs derived from patients using the EQ-5D (this was the only measure available for all outcomes)
2. Exclude if any of the following were found:
    a. The applicant found insufficient data to determine if the population "closely" or "broadly" approximated the VOYAGER PAD population
    b. The applicant found insufficient data to determine if the outcomes "closely" or "broadly" approximated the VOYAGER PAD outcomes
    c. The study was conducted outside the US, Canada, or Europe or the country was unknown
    d. Sample size was <20 subjects
3. Allow if no more than one of the following was found:
    a. The Applicant considered the population to "broadly" but not "closely" approximate the VOYAGER PAD population
    b. The Applicant considered the outcomes to "broadly" but not "closely" approximate the VOYAGER PAD outcomes
    c. The study was conducted in multiple countries

d. Sample size was not stated

4. If multiple HSUVs were provided in the same reference:
    a. Preference for HSUVs at 12 months post event or post-acute
    b. HSUVs provided by treatment arm or by subgroup were pooled based on the size of each group (when available) or by simple average

This algorithm has not been validated and other alternative algorithms may also reasonable.

Next, DSAS applied the proposed algorithm to the 373 HSUVs identified by the Applicant in their initial search (Seq 0442; June 25, 2021) to determine which matched the DSAS-proposed algorithm. This process produced 34 HSUVs (Table 6; Appendix Table A4) which were averaged by outcome to produce the mean HSUVs in Table 6.

Table 6. Mean HSUVs based on literature values included in the Applicant's submission that satisfy the DSAS-proposed algorithm.

Outcome	Mean HSUV (SD), n[A]	Mean weight[B]	Equivalent tradeoff[C]
Death	NA	1	1
Non-fatal ischemic stroke	0.68 (0.10), n=8	0.32	3.1
Non-fatal myocardial infarction	0.77 (0.15), n=14	0.23	4.3
Non-fatal acute limb ischemia	0.60 (0.26), n=7	0.40	2.5
Non-fatal major amputation	0.68 (0.29), n=2	0.33	3.1
Non-fatal major intracranial bleeding	0.69 (0.1), n=2	0.31	3.2
Non-fatal major non-intracranial bleeding	0.98 (NA), n=1	0.02	50.0

[A] n: number of published HSUVs included in the average
[B] Mean weight = 1 – Mean HSUV
[C] Equivalent tradeoff = 1 / Mean weight

Compared to Table 5, this set of literature values places significantly less weight on major amputation, intracranial bleeding, and major non-intracranial bleeding; slightly less weight on ischemic stroke; and slightly more weight on myocardial infarction and acute limb ischemia. The vales derived by DSAS are also closer to the weights generated by FDA respondents in Table 4; only the equivalent tradeoff for acute limb ischemia is outside the plausible range for all FDA respondents. DSAS utilized the mean HSUVs and weights from Table 6 in Section IV.c. below.

We recognize a number of limitations to our approach. First, starting with the Applicant's 373 HSUVs assumes their systematic literature search was complete. In fact, a *de novo* systematic literature search would likely have identified additional HSUVs for consideration. Second, due to time constraints, DSAS did not verify the accuracy of the information supplied by the Applicant for the HSUVs. Third, a statistical meta-analysis model was not used to combine HSUVs for outcomes with more than one HSUV. The ISPOR task force recommends such an approach. We note that the Applicant also did not use a statistical model to combine HSUVs from multiple references.

b. wNCB results

The Applicant applied the weights from Table 5 in Monte Carlo simulations in order to simultaneously account for uncertainty in the weights and event rates. Results shown in Table 7, for the ITT population and ITT (until ECOD) data scope and using endpoints most consistent with DSAS's analysis, show that for each year of treatment, rivaroxaban prevents approximately 20 "death-equivalents" per 10,000 patients treated compared to placebo. The 95% confidence interval of this estimate includes zero.

Table 7. wNCB results: difference in death equivalents by outcome and overall.

Outcome	Rivaroxaban (rate per 10,000 pt-yrs)	Placebo (rate per 10,000 pt-yrs)	Rate difference (95% CI)[A]	Mean weight (Table 5)	Difference in death equivalents[B]
All-cause mortality	398.0	367.7	30.3 (-30.1, 90.7)	1.0	30.3
Non-fatal ischemic stroke	76.3	90.4	-14.1 (-42.6, 14.5)	0.35	-4.9
Non-fatal myocardial infarction	141.0	154.3	-13.3 (-51.5, 24.8)	0.22	-2.9
Non-fatal acute limb ischemia	191.1	291.3	-100.3 (-149.6, -50.9)	0.36	-36.1
Non-fatal major amputation	120.5	142.5	-21.9 (-57.9, 14.1)	0.59	-12.9
Non-fatal major intracranial bleeding	22.7	20.2	2.5 (-11.9, 17)	0.42	1.1
Non-fatal major non-intracranial bleeding	77.6	51.9	25.6 (0.5, 50.8)	0.22	5.6
			Difference in total death equivalents per 10,000 pt-yrs		-19.9
			(95% CI from Monte Carlo simulations)		(-99.8, 55.8)
			Percent of simulations where benefits outweigh risks		68.8%

[A] Rate difference: rivaroxaban – placebo

[B] Rate difference x mean weight

Source: Table 26 of the br-analysis.pdf; Seq 0433; May 27, 2021

One-way sensitivity analysis conducted by the Applicant for uncertainty in weights (over the statistical distribution defined by the mean and standard deviation of the literature HSUVs) showed that the results were only sensitive to uncertainty in the weight for acute limb ischemia (Figures 22-29 of the br-analysis.pdf; Seq 0433; May 27, 2021). Analysis of wNCB over time showed a general trend towards increasing benefit (Figures 48 of the br-analysis.pdf; Seq 0433; May 27, 2021).

The Applicant also conducted the same analysis using the composite of CV death and fatal bleeds instead of all-cause mortality and using the safety analysis population and the on-treatment data scope. While the definition of the fatal outcome did not significantly impact the results, use of the safety analysis population and the on-treatment data scope resulted in a nominally significant result in favor of rivaroxaban (Table 8).

Table 8. Summary of all wNCB models.

Fatal outcome	Population & data scope	Difference in death equivalents per 10,000 pt-yrs (95% CI)	Percent of simulations where benefits outweigh risks
CV death + fatal bleed	ITT & until ECOD	-13.7 (-85.3, 52.6)	64.4%
All-cause mortality	ITT & until ECOD	-19.9 (-99.8, 55.8)	68.8%
CV death + fatal bleed	Safety & on-treatment	-68.1 (-135.7, -7.9)	98.7%
All-cause mortality	Safety & on-treatment	-87.0 (-157.8, -23.1)	99.7%

Source: Table 30 of the br-analysis.pdf; Seq 0433; May 27, 2021

c. Comparison between FDA's MCDA and Applicant's wNCB

As the conclusions of the Applicant's analysis differ from DSAS's, we bridged the two methodologies as follows:

1. Using Applicant and DSAS HSUVs with MCDA
2. Using FDA's weights with wNCB
3. Using DSAS's HSUVs with wNCB

This bridging indicates the differences in conclusions between the Applicant's and DSAS's analysis are driven by differences in weights, not differences in methodologies. We did not perform Monte Carlo simulation for the bridging.

Figure 8, which uses the literature HSUV-derived weights (Tables 5-6) with MCDA, shows that the difference in total MCDA scores is above 0 for all timepoints, with a maximum at 36 months. This result is slightly higher than the result from FDA respondent B (Figure 2). Notably, when using the literature HSUV's identified by DSAS from the Applicant's submission, the results shift in favor of rivaroxaban.

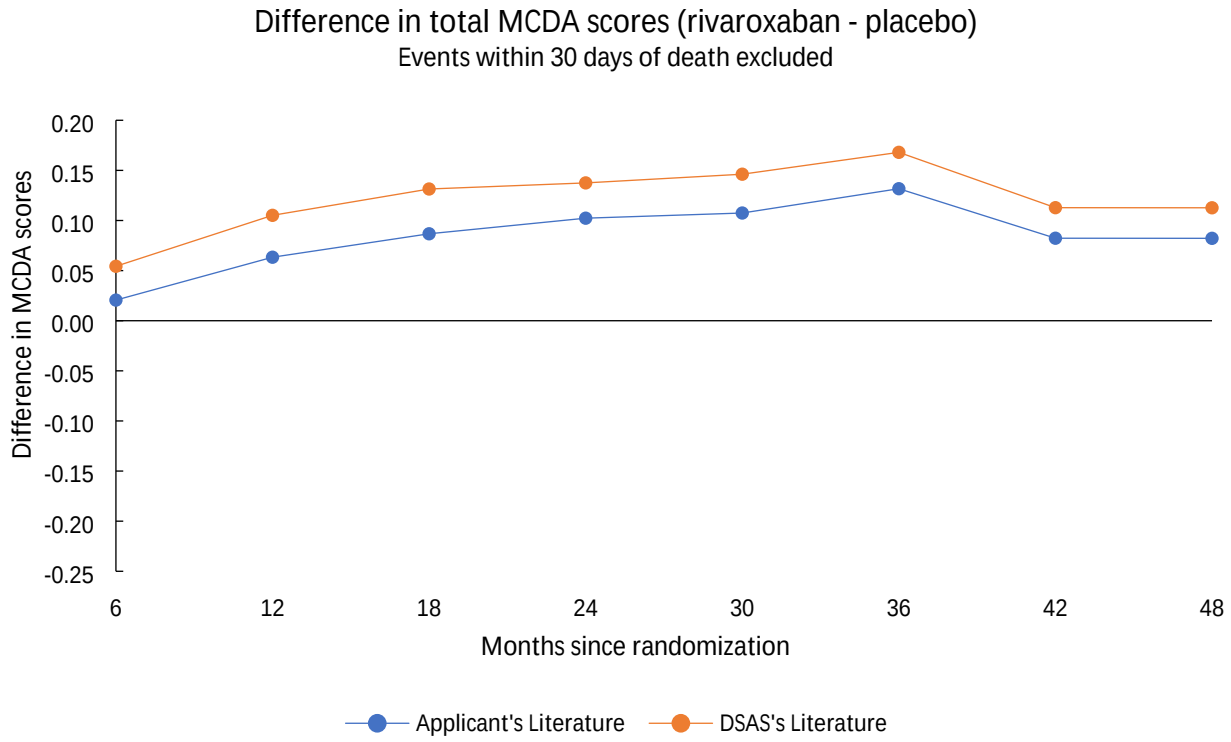

Figure 8. Difference in total MCDA scores utilizing HSUV-derived weights.

In Figure 9, which uses the FDA's tradeoff-derived weights in the Applicant's wNCB approach, we see that the difference in death equivalents per 10,000 pt-yrs favors rivaroxaban only for respondent B, with a minimum at 36 months. Small numbers of patients at risk at 42 and 48 months (Table 3), make these estimates less reliable and informative. This result is entirely consistent with the conclusions of FDA's MCDA (Figure 2).

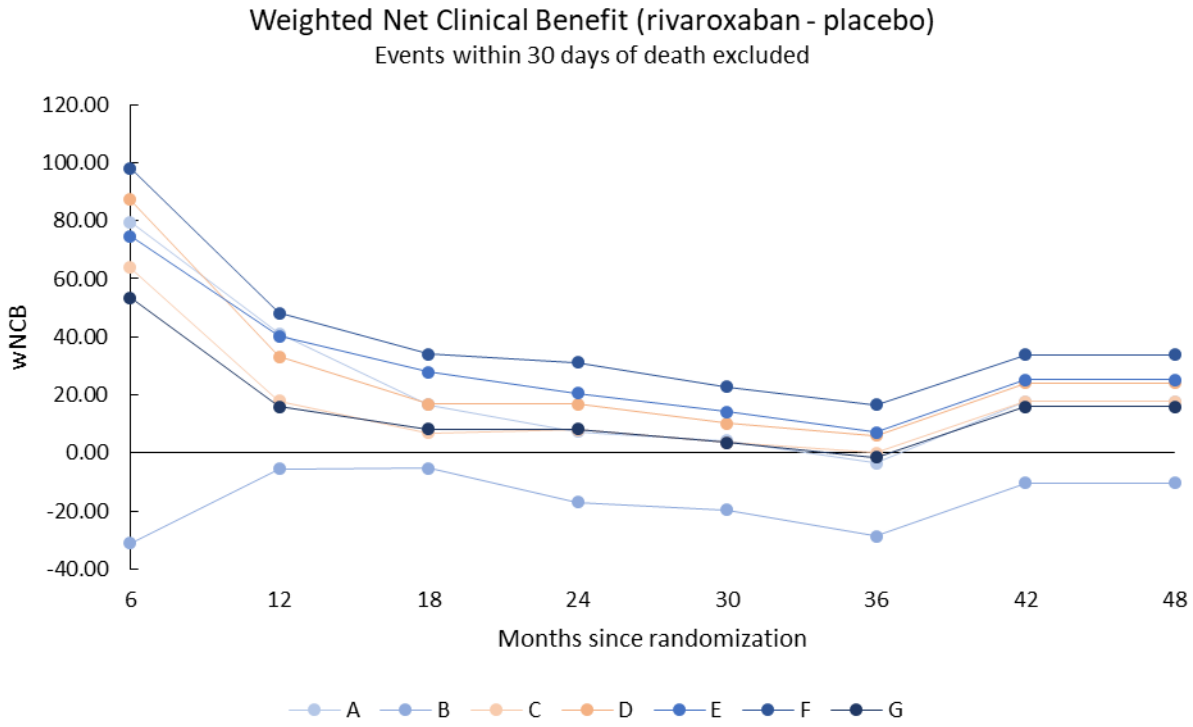

Figure 9. wNCB utilizing FDA's tradeoff-derived weights. Small numbers of patients at risk at 42 and 48 months (Table 3), make these estimates less reliable and informative.

Finally, Figure 10 shows the Applicant's wNCB approach based on both the Applicant's HSUVs and DSAS's HSUVs. Consistent with Figure 8, the results favor rivaroxaban for all timepoints and using the literature HSUV's identified by DSAS shifts the results in favor of rivaroxaban.

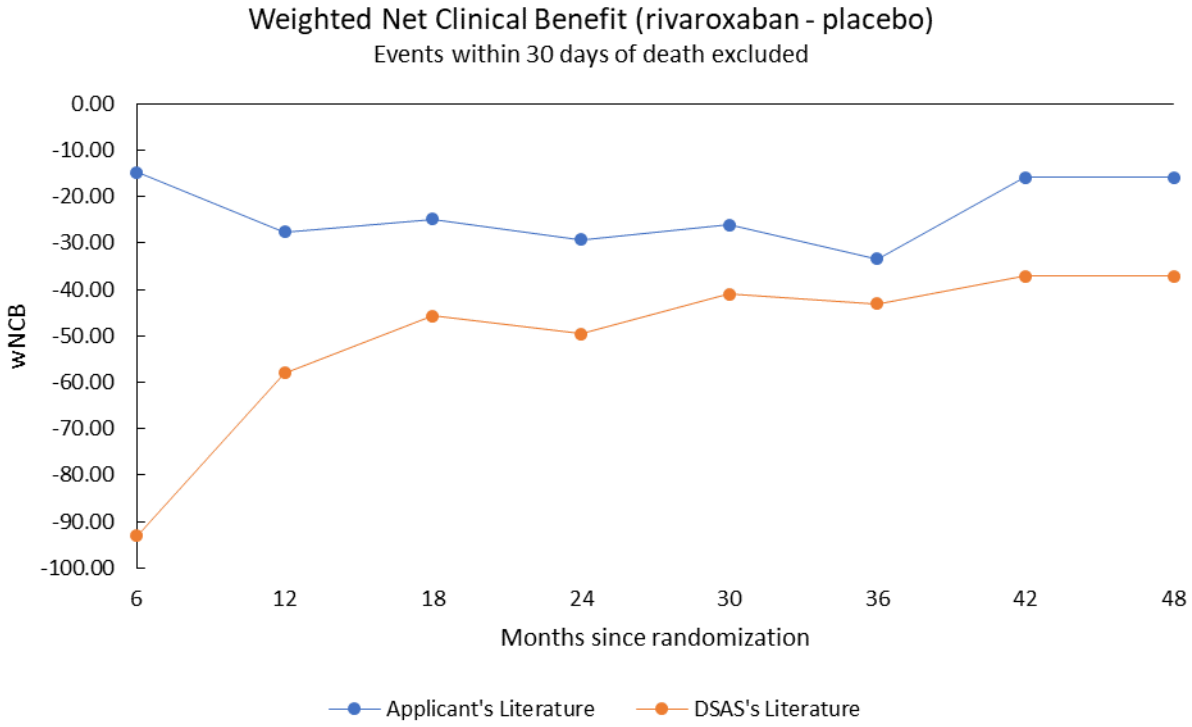

Figure 10. wNCB utilizing HSUV-derived weights from the Applicants' and DSAS's literature review. Small numbers of patients at risk at 42 and 48 months (Table 3), make these estimates less reliable and informative.

d. wNCB: Method Assessment

wNCB is a specific realization of MCDA that may be more intuitive for the decision-maker but is not as flexible as MCDA for different data types. As with MCDA, the method rests on numerical specification of the weights and tradeoffs between outcomes and the associated complexities. The Applicant's use of HSUVs potentially provides some generalizability for the weights.

V. Patient-level Benefit-Risk Analyses

In the initial application submitted (Seq 0385; October 23, 2020), the Applicant provided exploratory benefit-risk analyses which assessed excess differences in incidence rates and cumulative risk per 10,000 patients at landmark time points:

- The incidence rates were presented in forest plots for the first occurrence of the components of the primary efficacy and safety endpoints for both the intention-to-treat (ITT) and on-treatment populations.
- The Applicant also presented difference in Kaplan-Meier cumulative incidence rates at various landmark time-points based on the composite primary efficacy and safety endpoints for both the ITT and on-treatment populations.

In addition, Global Rank and Win Ratio analyses were conducted using the components of the primary efficacy endpoint as a sensitivity analysis for the primary efficacy endpoint.

For all benefit-risk analyses presented in the initial application, the Applicant concluded that the results supported a favorable benefit-risk profile for rivaroxaban compared to placebo.

Based on Agency's feedback in the 74-day filing letter, the Applicant submitted results for the following patient-level benefit-risk analyses (Seq 0433; May 27, 2021):

1. Global Rank
2. Win Ratio
3. Ordinal (or Ranked) DOOR
4. Weighted (or Partial Credit) DOOR

The Applicant also submitted results of a wNCB approach, discussed above in Section IV.

Three analysis sets were defined for use; however, not all three were used for each benefit-risk method:

1. ITT analysis set with ITT scope: The ITT analysis set (all unique randomized subjects) with the ITT scope (from randomization until the study efficacy-cut-off date [ECOD]); referred to as "ITT & until ECOD Data Scope"
2. Safety analysis set with the on-treatment data scope: The safety analysis set (all unique randomized subjects who took at least 1 dose of rivaroxaban or placebo study drug) with the on-treatment data scope (from randomization until the last dose of the study drug + 2 days); referred to as "Safety & On-treatment Data Scope"
3. ITT analysis set with a hybrid data scope: For efficacy outcomes, CV death and all-cause mortality, the ITT analysis set with the ITT data scope is used. TIMI major bleeding events were considered for the on-treatment data scope until ECOD (i.e., events from randomization until the earlier of the last day of intake of study drug + 2 days and ECOD); referred to as the "Hybrid Data Scope"

The results from all main analyses sets and data scopes will be presented in this document. The results for the analyses conducted over time and sensitivity analyses will be summarized in this document.

Although the results from the three analyses sets will be presented, it is generally preferred that analyses performed be based on the ITT & until ECOD Data Scope since this preserves the benefits of treatment randomization. This approach has the interpretation where one compares the risk of the outcome in subjects assigned to rivaroxaban compared to those assigned to placebo, regardless of treatment adherence, treatment discontinuation, or use of alternative therapies. The Safety & On-treatment Data Scope restricts, in this case, the subject information to the amount of time while receiving assigned treatment up to 2 days after permanent discontinuation. The Safety & On-treatment Data Scope would provide greater sensitivity for adverse events than the ITT & until ECOD Data Scope if the drug only increases the risk of the safety outcomes while subjects are on it and if subjects who adhere to the drug are comparable to subjects who adhere to placebo treatment. In the scenario where there is differential discontinuation between arms, then this approach could fail to detect an effect due to the lack of comparability between subjects remaining on treatment on the two arms.

a. Hierarchies for Global Rank and Win Ratio

The Applicant applied Global Rank and Win Ratio utilizing methodologies described by Dong et. al. (2016) and Follmann et. al. (2020) for eight hierarchies of clinical event outcomes. Table 9 shows four of the eight hierarchies (A1-A4). In addition, the Applicant included hierarchies B1-B4 (not shown in the table) which mirrored A1-A4 but replaced CV death with all-cause mortality.

Hierarchies A1-A2 are Applicant-determined and extensions of the initial analyses submitted with the sNDA to include TIMI major bleeding events.

Hierarchy A3 is based on the results of the HSUV literature review discussed in section IV on the Applicant's wNCB analysis.

Hierarchy A4 was developed as a sensitivity analysis to A3 where the rankings for non-fatal ALI and non-fatal IS were reversed because the utility values were similar.

Additionally, included in Table 9 is a hierarchy based on the HSUVs extracted by DSAS from the Applicant's submission (Table 6) and a hierarchy based on the tradeoff responses by FDA (Table 4). There are slight differences between these hierarchies compared to the various hierarchies used by the Applicant. The DSAS HSUV and FDA hierarchies have not been tested.

Table 9. Clinical Outcome Hierarchies used for Global Rank and Win Ratio Analyses. Colors are used to facilitate comparisons between hierarchies: the same outcome has the same color in each hierarchy; purple is for the least-desirable outcome in the FDA hierarchy and light yellow is for the most-desirable.

Rank	A1	A2	A3	A4	DSAS HSUV	FDA
1	CV Death[A] + TIMI fatal bleeding	CV Death[A] + TIMI fatal bleeding	CV Death[A] + TIMI fatal bleeding	CV Death[A] + TIMI fatal bleeding	CV Death[A] + TIMI fatal bleeding	CV Death[A] + TIMI fatal bleeding
2	ICH	ICH	Major Amputation	Major Amputation	ALI	ICH
3	IS	IS	ICH	ICH	Major Amputation	IS
4	ALI	ALI	ALI	IS	IS	MI
5	Major Amputation	MI	IS	ALI	ICH	Major Amputation
6	MI	Major Amputation	MI	MI	MI	ALI
7	Non-ICH TIMI major bleeding	Non-ICH TIMI major bleeding	Non-ICH TIMI major bleeding	Non-ICH TIMI major bleeding	Non-ICH TIMI major bleeding	Non-ICH TIMI major bleeding

[A] CV Death replaced with all-cause mortality to create hierarchies B1-B4
ALI = Acute Limb Ischemia; IS = Ischemic Stroke; ICH = Intracranial Hemorrhage.

VI. Global Rank

The Applicant completed Global Rank analyses using the three defined data scopes and eight varying hierarchies of clinical event outcomes. The results of all analyses, shown below in Tables 10-11, numerically favored rivaroxaban over placebo and were not sensitive to the specific hierarchies used. The most desirable outcome was assigned to the lowest score and the least desirable outcome was assigned the highest score with all intermediate scores increasing as outcome severity increased. The treatment group sum of stratified scores was lower than the placebo group indicating overall lower (i.e., more desirable) scores for the treatment group. Stratification was done by procedure type and clopidogrel use per IxRS assignment. The Van Elteren test, which is an extension of the Wilcoxon's rank-sum test for stratified data, tests the null hypothesis of no treatment effect in strata.

However, only the results based on the Safety & On-treatment Data Scope yielded nominally significant results.

The Applicant conducted Global Rank over time for hierarchy A1 only using the ITT & Until ECOD Data scope and noted that the p-values were similar to the corresponding Win Ratio p-values (Seq 0442, June 25, 2021).

See Appendix Table A5 for a description of the Global Rank Method.

Table 10. Global rank method to compare components of the primary efficacy outcome and TIMI major bleeding between treatment groups

Analysis set data scope	Hierarchy of the components of efficacy and safety outcomes	Stratified Sum of Scores	Expected Under H0	Standard Deviation Under H0	Z	Two-sided P-value
1: ITT analysis set, until ECOD	Hierarchy A1	1624.21	1639.00	7.8395	-1.8867	0.0592
	Hierarchy A2	1624.14	1639.00	7.8395	-1.8962	0.0579
	Hierarchy A3	1624.68	1639.00	7.8395	-1.8271	0.0677
	Hierarchy A4	1624.89	1639.00	7.8395	-1.8002	0.0718
2: ITT analysis set, efficacy until ECOD - on-treatment bleeding	Hierarchy A1	1623.89	1639.00	7.7653	-1.9462	0.0516
	Hierarchy A2	1623.83	1639.00	7.7653	-1.9534	0.0508
	Hierarchy A3	1624.35	1639.00	7.7653	-1.8861	0.0593
	Hierarchy A4	1624.55	1639.00	7.7653	-1.8615	0.0627
3: Safety analysis set, on-treatment data scope	Hierarchy A1	1599.50	1624.00	6.8383	-3.5827	0.0003
	Hierarchy A2	1599.43	1624.00	6.8383	-3.5934	0.0003
	Hierarchy A3	1599.71	1624.00	6.8383	-3.5521	0.0004
	Hierarchy A4	1599.86	1624.00	6.8383	-3.5307	0.0004

Source: Table 3 of the br-analysis.pdf; Seq 0433; May 27, 2021

Table 11. Global rank method to compare all-cause mortality and the components of the primary efficacy outcome, TIMI major bleeding between treatment groups

Analysis set data scope	Hierarchy of the components of efficacy and safety outcomes	Stratified Sum of Scores	Expected Under H0	Standard Deviation Under H0	Z	Two-sided P-value
1: ITT analysis set, until ECOD	Hierarchy B1	1626.56	1639.00	8.2752	-1.5037	0.1327
	Hierarchy B2	1626.48	1639.00	8.2752	-1.5134	0.1302
	Hierarchy B3	1627.08	1639.00	8.2752	-1.4400	0.1499
	Hierarchy B4	1627.25	1639.00	8.2752	-1.4194	0.1558
2: ITT analysis set, efficacy until ECOD - on-treatment bleeding	Hierarchy B1	1626.53	1639.00	8.2374	-1.5135	0.1301
	Hierarchy B2	1626.46	1639.00	8.2374	-1.5220	0.1280
	Hierarchy B3	1627.07	1639.00	8.2374	-1.4488	0.1474
	Hierarchy B4	1627.24	1639.00	8.2374	-1.4281	0.1533
3: Safety analysis set, on-treatment data scope	Hierarchy B1	1596.94	1624.00	7.0133	-3.8586	0.0001
	Hierarchy B2	1596.85	1624.00	7.0133	-3.8712	0.0001
	Hierarchy B3	1597.18	1624.00	7.0133	-3.8240	0.0001
	Hierarchy B4	1597.33	1624.00	7.0133	-3.8032	0.0001

Source: Table 4 of the br-analysis.pdf; Seq 0433; May 27, 2021

a. Global Rank: Method Assessment

The Global Rank method offers a straightforward approach and methodology to benefit-risk assessment with easily interpretable results. Similar to traditional time to event (TTE) analyses, only one event is considered in this methodology; however, unlike TTE which analyzes time to *first* event, the selected event for the Global Rank method is often selected as the worst clinical event based on the defined hierarchy in the specified time period. In the event of an event tie, time to an event or censoring can be considered in the ranking process.

VII. Win Ratio

The Applicant applied Win Ratio utilizing methodologies described by Dong et. al. (2016) and Follmann et. al. (2020), referred to as the “Dong Method” and the “Follmann Method”, respectively.

a. Win Ratio: The Dong Method

The Applicant completed Win Ratio analyses on the three defined data scopes and eight varying hierarchies of clinical event outcomes. The results for these analyses numerically favored rivaroxaban over placebo and were not sensitive to the choice of hierarchy; all results were greater than 1, meaning that the number of wins for was greater than the losses for the treatment group compared to the placebo group. Only the results in the Safety & On-treatment Data Scope yielded nominally significant results. Tables 12-13 provide the results.

See Appendix Table A6 for a description of the Win Ratio Method as described by Dong.

Table 12. Win ratio rivaroxaban versus placebo for the components of the primary efficacy outcome and TIMI major bleeding based on the method by Dong

Analysis set data scope	Hierarchy of the components of efficacy and safety outcomes	Win ratio Rivaroxaban versus Placebo (95% CI) (a)	Two-sided P-value (Chi-squared test) (a)
1: ITT analysis set, until ECOD	Hierarchy A1	1.12 (0.99; 1.26)	0.0620
	Hierarchy A2	1.12 (1.00; 1.26)	0.0598
	Hierarchy A3	1.11 (0.99; 1.25)	0.0692
	Hierarchy A4	1.11 (0.99; 1.25)	0.0729
2: ITT analysis set, efficacy until ECOD - on-treatment bleeding	Hierarchy A1	1.12 (1.00; 1.27)	0.0502
	Hierarchy A2	1.13 (1.00; 1.27)	0.0484
	Hierarchy A3	1.12 (1.00; 1.26)	0.0562
	Hierarchy A4	1.12 (1.00; 1.26)	0.0590
3: Safety analysis set, on-treatment data scope	Hierarchy A1	1.26 (1.09; 1.44)	0.0011
	Hierarchy A2	1.26 (1.10; 1.44)	0.0011
	Hierarchy A3	1.26 (1.09; 1.44)	0.0012
	Hierarchy A4	1.25 (1.09; 1.44)	0.0012

Source: Table 5 of the br-analysis.pdf; Seq 0433; May 27, 2021

Table 13. Win ratio rivaroxaban versus placebo for all-cause mortality and components of the primary efficacy outcome, TIMI major bleeding based on the method by Dong

Analysis set data scope	Hierarchy of the components of efficacy and safety outcomes	Win ratio Rivaroxaban versus Placebo (95% CI) (a)	Two-sided P-value (Chi-squared test) (a)
1: ITT analysis set, until ECOD	Hierarchy B1	1.09 (0.97; 1.21)	0.1335
	Hierarchy B2	1.09 (0.98; 1.21)	0.1296
	Hierarchy B3	1.08 (0.97; 1.21)	0.1460
	Hierarchy B4	1.08 (0.97; 1.21)	0.1523
2: ITT analysis set, efficacy until ECOD - on-treatment bleeding	Hierarchy B1	1.09 (0.98; 1.22)	0.1211
	Hierarchy B2	1.09 (0.98; 1.22)	0.1177
	Hierarchy B3	1.09 (0.97; 1.21)	0.1325
	Hierarchy B4	1.09 (0.97; 1.21)	0.1381
3: Safety analysis set, on-treatment data scope	Hierarchy B1	1.27 (1.11; 1.45)	0.0005
	Hierarchy B2	1.27 (1.11; 1.45)	0.0005
	Hierarchy B3	1.27 (1.11; 1.45)	0.0005
	Hierarchy B4	1.27 (1.11; 1.45)	0.0006

Source: Table 6 of the br-analysis.pdf; Seq 0433; May 27, 2021

b. Win Ratio: Method Assessment (The Dong Method)

Win Ratio (Dong Method) offers a straightforward approach to benefit-risk assessment with easily interpretable results. The Win Ratio can be interpreted as the relative measure of treatment benefit (Evans et. al., 2020). This approach uses pairwise comparisons of all subjects in the treatment and placebo groups.

The Applicant used the unmatched pair method which can produce unfair comparisons, both for and against treatment, which can result in the dilution of the Win Ratio nearer to 1 (Pocock 2012). A Win Ratio of 1 can be interpreted as a tie between wins and losses for treatment.

For each pairwise comparison, the worst clinical event to have occurred to each subject based on a defined hierarchy and common, pairwise follow-up time is compared. For a clinical event tie, time is used determine the "winner" and "loser" where the subject with the event occurring later is the winner.

c. Win Ratio: Follmann Method

The Win Ratio methodology proposed by Follmann et al 2020, creates ordering scores based on events, as defined by the hierarchies in Table 9, and incorporate the time of event or censoring in the analysis. The data is constructed in a similar manner to multiple interval censoring, with a subject included in each discrete follow-up time period, until an event occurs. The Win Ratio is then estimated using a Cox proportional hazards regression model and the hazard ratio can be interpreted as the win ratio. Point estimates greater than 1 can be interpreted as relative treatment benefit of the treatment compared to placebo.

See Appendix Table A7 for a description of the Win Ratio Method as described by Follmann.

The results for all analyses numerically favored rivaroxaban over placebo and were not sensitive to the specific hierarchy (Tables 14-15). However, only the results based on the Safety & On-treatment Data Scope yielded nominally significant results.

Table 14. Win ratio estimations for components of the primary efficacy outcome and TIMI major bleeding applying Cox regression on ordering scores based on the method by Follmann

Analysis set data scope	Hierarchy of the components of efficacy and safety outcomes	Win ratio Rivaroxaban versus Placebo (95% CI) (a)	Two-sided P-value (a)
1: ITT analysis set, until ECOD	Hierarchy A1	1.12 (1.00; 1.26)	0.0476
	Hierarchy A2	1.12 (1.00; 1.26)	0.0468
	Hierarchy A3	1.12 (1.00; 1.25)	0.0511
	Hierarchy A4	1.12 (1.00; 1.25)	0.0533
2: ITT analysis set, efficacy until ECOD - on-treatment bleeding	Hierarchy A1	1.12 (1.00; 1.26)	0.0467
	Hierarchy A2	1.12 (1.00; 1.26)	0.0461
	Hierarchy A3	1.12 (1.00; 1.26)	0.0502
	Hierarchy A4	1.12 (1.00; 1.26)	0.0522
3: Safety analysis set, on-treatment data scope	Hierarchy A1	1.25 (1.09; 1.43)	0.0012
	Hierarchy A2	1.25 (1.09; 1.43)	0.0012
	Hierarchy A3	1.25 (1.09; 1.43)	0.0012
	Hierarchy A4	1.25 (1.09; 1.43)	0.0013

Source: Table 7 of the br-analysis.pdf; Seq 0433; May 27, 2021

Table 15. Win ratio estimations for all-cause mortality and components of the primary efficacy outcome, TIMI major bleeding applying Cox regression on ordering scores based on the method by Follmann

Analysis set data scope	Hierarchy of the components of efficacy and safety outcomes	Win ratio Rivaroxaban versus Placebo (95% CI) (a)	Two-sided P-value (a)
1: ITT analysis set, until ECOD	Hierarchy B1	1.09 (0.98; 1.22)	0.1003
	Hierarchy B2	1.09 (0.98; 1.22)	0.0991
	Hierarchy B3	1.09 (0.98; 1.21)	0.1069
	Hierarchy B4	1.09 (0.98; 1.21)	0.1102
2: ITT analysis set, efficacy until ECOD - on-treatment bleeding	Hierarchy B1	1.09 (0.98; 1.22)	0.1001
	Hierarchy B2	1.09 (0.98; 1.22)	0.0991
	Hierarchy B3	1.09 (0.98; 1.22)	0.1068
	Hierarchy B4	1.09 (0.98; 1.21)	0.1102
3: Safety analysis set, on-treatment data scope	Hierarchy B1	1.26 (1.11; 1.44)	0.0005
	Hierarchy B2	1.26 (1.11; 1.44)	0.0005
	Hierarchy B3	1.26 (1.11; 1.44)	0.0005
	Hierarchy B4	1.26 (1.11; 1.44)	0.0005

Source: Table 8 of the br-analysis.pdf; Seq 0433; May 27, 2021

d. Win Ratio Over Time: The Follmann Method

The Applicant applied the Win Ratio over time using the Follmann Method by censoring subjects at the following time points: 30 days, 60 days, 90 days, 180 days, 270 days, 365 days (1 year), 540 days (1.5 years), 730 days (2 years), 900 days (2.5 years), 1,095 days (3 years), 1,270 days (3.5 years), and 1,460 days (4 years).

Overall, the results generally favored rivaroxaban over placebo numerically and the ratios remained relatively constant over the increasing time points. For a couple of time points in the ITT & ECOD Data Scope the Win Ratio dropped below 1, meaning the placebo had more "wins" than "losses" compared to rivaroxaban.

e. Win Ratio: Method Assessment (The Follmann Method)

The Win Ratio Follmann Method addresses potential shortcomings in the Global Rank and Win Ratio (Dong Method) by including censoring time for subjects without events in the overall ordering. However, this method, like Global Rank and Win Ratio (Dong Method), will only incorporate one event per subject. This event will often be chosen as the worst event per the defined hierarchy.

VIII. Ordinal Desirability of Outcome Ranking (DOOR)

The Applicant conducted Ordinal DOOR using the three scenarios shown in Table 16. Direct comparison to the tradeoffs supplied by FDA respondents (Table 4) is challenging given the range of clinical outcomes included in each category. However, FDA's responses would likely be most consistent with DOOR Scenario #2. None of the scenarios agree well with the literature HSUVs (Tables 5-6).

Two data scopes were used in the ordinal DOOR analysis:
1. ITT & until ECOD Data Scope
2. Safety & On-treatment Data Scope

Table 16. DOOR Scenarios. Colors and bolding are used to facilitate comparisons between hierarchies: the same outcome has the same color in each hierarchy; purple is for the least-desirable outcome and green is for the most-desirable; bold text is used for outcomes with more than 1 event.

Rank	DOOR Scenario #1	DOOR Scenario #2	DOOR Scenario #3
1	Survive, no events listed below	Survive, no events listed below	Survive, no events listed below
2	Survive, 1 ALI or non-ICH TIMI MB	Survive, 1 non-ICH TIMI MB	Survive, 1 non-ICH TIMI MB
3	Survive, >1 ALI or non-ICH TIMI MB	Survive, 1 ALI	Survive, 1 ALI, MI, ischemic stroke, ICH, or major amputation (all non-fatal)
4	Survive, 1 MI, ischemic stroke, ICH, or major amputation (all non-fatal)	Survive, >1 ALI or non-ICH TIMI MB	Survive, >1 ALI, MI, ischemic stroke, ICH, or major amputation (all non-fatal)
5	Survive, >1 MI, ischemic stroke, ICH, or major amputation (all non-fatal)	Survive, 1 MI, ischemic stroke, ICH, or major amputation (all non-fatal)	All-cause death
6	All-cause death	Survive, >1 MI, ischemic stroke, ICH, or major amputation (all non-fatal)	
7		All-cause death	

ALI = Acute Limb Ischemia, ICH = Intracranial hemorrhage, MI = Myocardial infarction

Additional sensitivity analysis was completed on both data scopes in which time was used as a tie breaker for the scenario "Survive, no events listed below" where the winner was the subject remaining in the trial longer without any listed harmful events.

Tables 17-18 provide the results of Ordinal DOOR. The analyses using the ITT & until ECOD Data Scope found the DOOR probabilities ranged from 0.506 to 0.507 with the 95% confidence intervals including probabilities lower than 0.500. The DOOR probabilities were higher with the Safety & On-treatment Data Scope, with ranges from 0.516 to 0.517; all corresponding 95% confidence intervals were greater than 0.500. As a probability greater than 0.5 suggests the treatment is preferred, these results indicate rivaroxaban may be preferred over placebo.

See Appendix Table A8 for a description of the Ordinal DOOR Method.

Table 17. DOOR outcomes and probability by treatment and scenario set; ITT Set/until ECOD data scope

	Rivaroxaban + ASA (N=3286) n(%)	Placebo + ASA (N=3278) n(%)	Proportion difference % (95% CI)	DOOR probability (95% CI)
Scenario set 1				
Survive, no events listed below	2631 (80.1)	2570 (78.4)	1.7 (-0.3, 3.6)	0.506 (0.493, 0.520)
Survive, 1 ALI or non-ICH TIMI major bleeding	97 (3.0)	132 (4.0)	-1.1 (-2.0, -0.2)	
Survive, >1 ALI or non-ICH TIMI major bleeding	24 (0.7)	29 (0.9)	-0.2 (-0.6, 0.3)	
Survive, 1 MI, ischemic stroke, ICH, or major amputation	189 (5.8)	222 (6.8)	-1.0 (-2.2, 0.2)	
Survive, >1 MI, ischemic stroke, ICH, or major amputation	24 (0.7)	28 (0.9)	-0.1 (-0.6, 0.3)	
All-cause death	321 (9.8)	297 (9.1)	0.7 (-0.7, 2.1)	
Scenario set 2				
Survive, no events listed below	2631 (80.1)	2570 (78.4)	1.7 (-0.3, 3.6)	0.507 (0.493, 0.521)
Survive, 1 non-ICH TIMI major bleeding	31 (0.9)	18 (0.5)	0.4 (-0.0, 0.8)	
Survive, 1 ALI	66 (2.0)	114 (3.5)	-1.5 (-2.3, -0.7)	
Survive, >1 ALI or non-ICH TIMI major bleeding	24 (0.7)	29 (0.9)	-0.2 (-0.6, 0.3)	
Survive, 1 MI, ischemic stroke, ICH, or major amputation	189 (5.8)	222 (6.8)	-1.0 (-2.2, 0.2)	
Survive, >1 MI, ischemic stroke, ICH, or major amputation	24 (0.7)	28 (0.9)	-0.1 (-0.6, 0.3)	
All-cause death	321 (9.8)	297 (9.1)	0.7 (-0.7, 2.1)	
Scenario set 3				
Survive, no events listed below	2631 (80.1)	2570 (78.4)	1.7 (-0.3, 3.6)	0.507 (0.493, 0.521)
Survive, 1 or >1 non-ICH TIMI major bleeding	34 (1.0)	19 (0.6)	0.5 (0.0, 0.9)	
Survive, 1 ALI, MI, ischemic stroke, ICH, or major amputation	226 (6.9)	299 (9.1)	-2.2 (-3.6, -0.9)	
Survive, >1 ALI, MI, ischemic stroke, ICH, or major amputation	74 (2.3)	93 (2.8)	-0.6 (-1.3, 0.2)	
All-cause death	321 (9.8)	297 (9.1)	0.7 (-0.7, 2.1)	

Source: Table 11 of the br-analysis.pdf; Seq 0433; May 27, 2021

Table 18. DOOR outcomes and probability by treatment and scenario set: Safety Analysis Set/On-treatment data scope

	Rivaroxaban + ASA (N=3256) n(%)	Placebo + ASA (N=3248) n(%)	Proportion difference % (95% CI)	DOOR probability (95% CI)
Scenario set 1				
Survive, no events listed below	2852 (87.6)	2739 (84.3)	3.3 (1.6, 5.0)	0.516 (0.502, 0.530)
Survive, 1 ALI or non-ICH TIMI major bleeding	111 (3.4)	144 (4.4)	-1.0 (-2.0, -0.1)	
Survive, >1 ALI or non-ICH TIMI major bleeding	15 (0.5)	21 (0.6)	-0.2 (-0.5, 0.2)	
Survive, 1 MI, ischemic stroke, ICH, or major amputation	168 (5.2)	199 (6.1)	-1.0 (-2.1, 0.2)	
Survive, >1 MI, ischemic stroke, ICH, or major amputation	8 (0.2)	21 (0.6)	-0.4 (-0.7, -0.1)	
All-cause death	102 (3.1)	124 (3.8)	-0.7 (-1.6, 0.2)	
Scenario set 2				
Survive, no events listed below	2852 (87.6)	2739 (84.3)	3.3 (1.6, 5.0)	0.516 (0.502, 0.530)
Survive, 1 non-ICH TIMI major bleeding	33 (1.0)	17 (0.5)	0.5 (0.1, 0.9)	
Survive, 1 ALI	78 (2.4)	127 (3.9)	-1.5 (-2.4, -0.7)	
Survive, >1 ALI or non-ICH TIMI major bleeding	15 (0.5)	21 (0.6)	-0.2 (-0.5, 0.2)	
Survive, 1 MI, ischemic stroke, ICH, or major amputation	168 (5.2)	199 (6.1)	-1.0 (-2.1, 0.2)	
Survive, >1 MI, ischemic stroke, ICH, or major amputation	8 (0.2)	21 (0.6)	-0.4 (-0.7, -0.1)	
All-cause death	102 (3.1)	124 (3.8)	-0.7 (-1.6, 0.2)	
Scenario set 3				
Survive, no events listed below	2852 (87.6)	2739 (84.3)	3.3 (1.6, 5.0)	0.517 (0.503, 0.531)
Survive, 1 or >1 non-ICH TIMI major bleeding	35 (1.1)	17 (0.5)	0.6 (0.1, 1.0)	
Survive, 1 ALI, MI, ischemic stroke, ICH, or major amputation	226 (6.9)	302 (9.3)	-2.4 (-3.7, -1.0)	
Survive, >1 ALI, MI, ischemic stroke, ICH, or major amputation	41 (1.3)	66 (2.0)	-0.8 (-1.4, -0.2)	
All-cause death	102 (3.1)	124 (3.8)	-0.7 (-1.6, 0.2)	

Source: Table 12 of the br-analysis.pdf; Seq 0433; May 27, 2021

a. Ordinal DOOR Over Time

The Applicant also conducted Ordinal DOOR over time by censoring subjects every three months from randomization for the first year and then biannually thereafter.

The point estimates for the ITT & until ECOD Data Scope analysis revealed generally consistent results which were just above 0.50. The Safety & On-treatment Data Scope analysis had higher point estimates which ranged from 0.50 to 0.52 but showed an upward trend overtime. The majority of the lower bounds of the 95% confidence intervals from both data scopes were below 0.50.

b. Ordinal DOOR: Method Assessment

Unlike Global Rank and Win Ratio, DOOR analysis can include multiple clinical events in the composition of clinical scenarios. This is a strength of DOOR over both Global Rank and Win Ratio as well as time-to-event analysis which analyze time to first (or in some cases worst) event only. The use of rankings offers a straightforward means to conduct the analysis and enables multiple scenarios to be tested for sensitivity.

The timing of events is generally not considered, only the event or combination of events to have occurred over the timeframe of interest is included. However, in the sensitivity analyses, the Applicant did use censor time for subjects in the “Survive, No Events Listed” category.

IX. Weighted (Partial Credit) DOOR

The Applicant performed Weighted DOOR using the three scenarios set forth in the analysis proposal. See Table 16 for the scenarios used. Two data scopes were used in the analysis:

1. ITT & until ECOD Data Scope
2. Safety & On-treatment Data Scope

Weighted DOOR utilizes weights, termed partial credits, where the highest score, 100, is assigned to the best event, in this case “Survive, No Events Listed” and the lowest score, 0, is assigned to the worst event, “All-cause Death”. The weights were obtained using structured interviews with six cardiovascular physicians and surgeons affiliated with the Applicant but not involved with the VOYAGER PAD development program. Figure 11 provides the responses from each of the six respondents for the selected scenarios.

Comparison to the tradeoffs provided by FDA respondents (Table 4) is challenging given the range of clinical outcomes included in each category and the range of tradeoffs provided by FDA respondents for those outcomes. In particular, categories combining ALI, MI, ischemic stroke, ICH, and amputation would be challenging to specify a single partial credit for based on the FDA tradeoffs. Combination of events makes comparison to the literature HSUVs (Tables 5-6) challenging but there appears to be poor agreement.

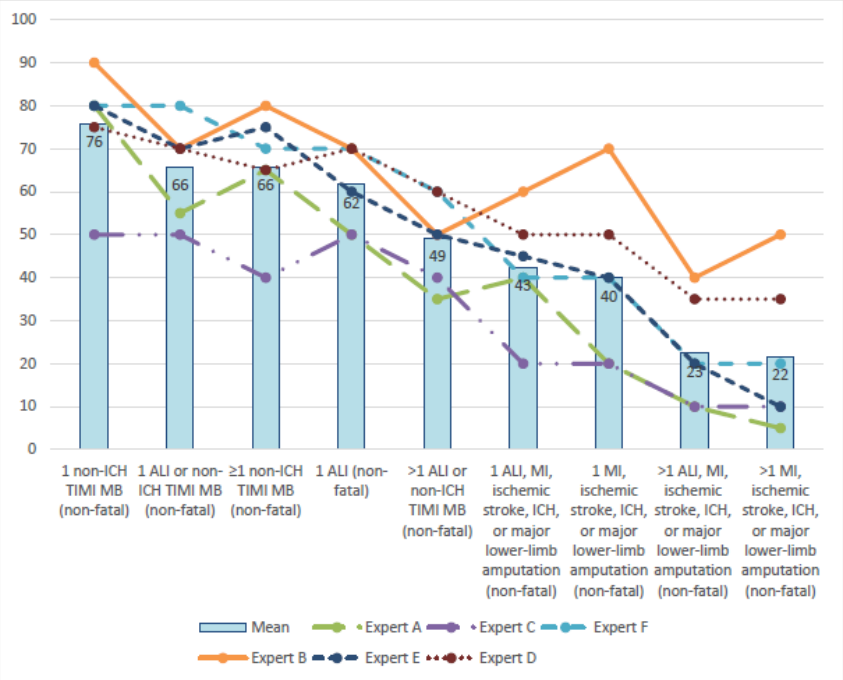

Figure 11. Partial Credits for Each DOOR Scenario based on Structured Interviews.
Source: Figure 9; br-analysis.pdf; Seq 0433; May 27, 2021

For the two data scopes, the Applicant calculated the difference in average scores for both rivaroxaban and placebo groups, along with 95% confidence intervals. The results are provided in Tables 19-20.

Based on the ITT & until ECOD Data Scope, the point estimates ranged from 0.445 to 0.866 and were not statistically significant since the 95% confidence bounds included 0. The point estimates can be interpreted as treating 1,000 patients with rivaroxaban on average results in the partial credit equivalent of 4 to 8 more subjects surviving compared to placebo.

Based on the Safety & On-treatment Data Scope, the point estimates were nominally significant and ranged from 2.021 to 2.436. The point estimates can be interpreted as treating 1,000 patients with rivaroxaban on average results in the partial credit equivalent of 20 to 24 more subjects surviving compared to placebo.

See Appendix Table A9 for a description of the Weighted DOOR Method.

Table 19. Partial credit (weighted DOOR) analysis summary; ITT Analysis Set/until ECOD Data Scope

	Proportion Difference % Rivaroxaban vs Placebo	Partial Credit	Contribution	Rivaroxaban + ASA Mean (SD)	Placebo + ASA Mean(SD)	Difference in mean (95% CI)
Scenario set 1						
Survive, no events listed below	1.7	100	1.70	84.83(32.432)	84.39(32.063)	0.445
Survive, 1 ALI or non-ICH TIMI major bleeding	-1.1	66	-0.73			(-1.116, 2.005)
Survive, >1 ALI or non-ICH TIMI major bleeding	-0.2	49	-0.10			
Survive, 1 MI, ischemic stroke, ICH, or major amputation	-1.0	40	-0.40			
Survive, >1 MI, ischemic stroke, ICH, or major amputation	-0.1	22	-0.02			
All-cause death	0.7	0	0.00			
Scenario set 2						
Survive, no events listed below	1.7	100	1.70	84.85(32.443)	84.31(32.128)	0.543
Survive, 1 non-ICH TIMI major bleeding	0.4	76	0.30			(-1.019, 2.105)
Survive, 1 ALI	-1.5	62	-0.93			
Survive, >1 ALI or non-ICH TIMI major bleeding	-0.2	49	-0.10			
Survive, 1 MI, ischemic stroke, ICH, or major amputation	-1.0	40	-0.40			
Survive, >1 MI, ischemic stroke, ICH, or major amputation	-0.1	22	-0.02			
All-cause death	0.7	0	0.00			
Scenario set 3						
Survive, no events listed below	1.7	100	1.70	84.23(33.125)	83.36(33.177)	0.866
Survive, 1 or >1 non-ICH TIMI major bleeding	0.5	66	0.33			(-0.738, 2.471)
Survive, 1 ALI, MI, ischemic stroke, ICH, or major amputation	-2.2	43	-0.95			
Survive, >1 ALI, MI, ischemic stroke, ICH, or major amputation	-0.6	23	-0.14			
All-cause death	0.7	0	0.00			

Source: Table 16 of the br-analysis.pdf; Seq 0433; May 27, 2021

Table 20. Partial credit (weighted DOOR) analysis summary; Safety Analysis Set/On-treatment Data Scope

	Proportion Difference % Rivaroxaban vs Placebo	Partial Credit	Contribution	Rivaroxaban + ASA Mean (SD)	Placebo + ASA Mean(SD)	Difference in mean (95% CI)
Scenario set 1						
Survive, no events listed below	3.3	100	3.30	92.19(22.460)	90.16(24.763)	2.021
Survive, 1 ALI or non-ICH TIMI major bleeding	-1.0	66	-0.66			(0.872, 3.170)
Survive, >1 ALI or non-ICH TIMI major bleeding	-0.2	49	-0.10			
Survive, 1 MI, ischemic stroke, ICH, or major amputation	-1.0	40	-0.40			
Survive, >1 MI, ischemic stroke, ICH, or major amputation	-0.4	22	-0.09			
All-cause death	-0.7	0	0.00			
Scenario set 2						
Survive, no events listed below	3.3	100	3.30	92.19(22.485)	90.06(24.887)	2.131
Survive, 1 non-ICH TIMI major bleeding	0.5	76	0.38			(0.978, 3.284)
Survive, 1 ALI	-1.5	62	-0.93			
Survive, >1 ALI or non-ICH TIMI major bleeding	-0.2	49	-0.10			
Survive, 1 MI, ischemic stroke, ICH, or major amputation	-1.0	40	-0.40			
Survive, >1 MI, ischemic stroke, ICH, or major amputation	-0.4	22	-0.09			
All-cause death	-0.7	0	0.00			
Scenario set 3						
Survive, no events listed below	3.3	100	3.30	91.58(23.560)	89.14(26.319)	2.436
Survive, 1 or >1 non-ICH TIMI major bleeding	0.6	66	0.40			(1.222, 3.650)
Survive, 1 ALI, MI, ischemic stroke, ICH, or major amputation	-2.4	43	-1.03			
Survive, >1 ALI, MI, ischemic stroke, ICH, or major amputation	-0.8	23	-0.18			
All-cause death	-0.7	0	0.00			

Source: Table 17 of the br-analysis.pdf; Seq 0433; May 27, 2021

The Applicant also completed various sensitivity analyses for Weighted DOOR, including:

1. Monte Carlo simulation in which all statistical uncertainty in the clinical data is assessed. The Applicant concluded that the probability point estimate of results favoring rivaroxaban to placebo ranged from 71.51% to 100.00% for the two data scopes used.
2. One-way grid search in which the impact of varying the partial credit of each scenario independently is assessed. The Applicant concluded that the tipping point, or the point

where the results would favor placebo over rivaroxaban, were outside the plausible range or "far from the observed partial credit", revealing a positive result for rivaroxaban.

3. Two-way grid search in which the impact of varying the partial credits of pairs of scenarios is assessed. The Applicant concluded that the tipping point line was either out of plausible range or "distant from the partial credits provided by all clinical experts other than for expert B" for the ITT & until ECOD Data Scope. Expert B's partial credits were noted as being away from the other data points, indicating an outlier, or near the tipping point for several 2-way grid search involving the scenario "1 MI, ischemic stroke, ICH, or major lower-limb amputation (non-fatal)". The tipping points for the Safety & On-treatment Data Scope were all out of plausible ranges.

a. Weighted DOOR over time

The Applicant assessed Weighted DOOR over time by calculating the mean partial credits from randomization up to every 90 days for the first year and 180 days thereafter for the three scenarios and the ITT & until ECOD and Safety & On-treatment Data Scopes. For the ITT & until ECOD Data Scope, the results for all three scenarios trend upwards overtime, ranging from approximately -0.1 to 1.0 with all 95% confidence bounds including estimates below zero.

For the Safety & On-treatment Data Scope, the results for all three scenarios are higher than the ITT & until ECOD Data Scope and trend upwards overtime, ranging from approximately 0.5 to 2.5 with the majority of the 95% confidence bounds greater than zero.

b. Weighted DOOR: Method Assessment

Unlike Global Rank and Win Ratio (both methods as described by Dong and Follmann), DOOR analysis can include multiple clinical events in the composition of clinical scenarios. This is a strength of DOOR over both Global Rank and Win Ratio as well as time-to-event analysis which analyzing time to first (or in some cases worst) event only.

In addition, Weighted DOOR includes expert opinion through the partial credits or weights that are used in the analysis. Weighted DOOR can account for unequal incremental desirability of the clinical outcome(s); this is distinct from Global Rank, Win Ratio (both methods), and Ranked DOOR.

The timing of events is not considered, only the event or combination of events to have occurred over the timeframe of interest is included.

X. Observations regarding the Applicant's submission

It is important to recognize the exploratory nature of the analyses discussed in this review, both those conducted by DSAS and by the Applicant. As one objective is to better understand the methodology, some additional flexibility may be appropriate than is normally afforded analyses conducted by the Applicant. Ideally, analyses and weights would be fully pre-specified before trial results were available and the Agency should be provided to opportunity to comment on the Applicant's prespecified analysis plan. This pre-specification should also include a plan for how additional outcomes would be incorporated if, for example, unexpected safety outcomes were identified during the trial.

Notwithstanding this caveat, DSAS has the following specific observations on the Applicant's submission which may be useful to future FDA reviewers.

a. Source of weights

The Applicant originally proposed three sources of information for the weights: a literature review, results from a physician preference survey, and analysis of EQ-5D data collected as part of the VOYAGER PAD trial (email to the RPM on Feb 19, 2021; Seq 0451, July 29, 2021). In the end, only literature HSUVs were supplied and a non-pre-specified interview study was submitted.

Literature results are discussed at length above in Section IV.a. In our opinion, for future contexts, FDA should consider whether the ISPOR task force recommendations (Brazier 2019) should be provided to Applicants to guide their literature reviews for HSUVs. In addition, FDA may decide to review the source literature in addition to reviewing the assessment provided by the applicant, although we note that this may be challenging within the time constraints of a review.

The physician preference survey was designed and partially fielded by the Applicant but interim analysis of 63 responses were either "non-sensible" or "not sufficiently differentiated" to support use (Seq 0442; June 25, 2021). This points strongly to the difficulty of designing survey instruments. All plans for conducting surveys should build in adequate time for cognitive testing and revision. The FDA Patient-Focused Drug Development (PFDD) Guidance provides general advice on the design and fielding of surveys (FDA 2020). In addition to the design issues, DSAS notes that the Applicant's plan to target cardiovascular physicians and surgeons represents only a small portion of the clinical community that will care for patients with PAD and manage the possible bleeding events caused by a drug like rivaroxaban. As a result, even if the survey was successful, the preferences would have represented the preferences only of the physicians most likely to prescribe rivaroxaban and not all physicians. Ideally, Sponsors will discuss the target population for any preference study (physician, patient, or otherwise) with the Agency before designing the study.

As a result of the challenges with the physician preference survey, the Applicant conducted structured interviews with six cardiologists to obtain weights for the weighted DOOR analysis. These interviews are not unlike the process DSAS applied for obtaining FDA tradeoffs and structured interviews is one of many reasonable approaches for Applicants to obtain weights for benefit-risk analyses. For clarity, we note some points for consideration for future cases where interviews are employed. First, plans for interviews should be pre-specified and the interview guide supplied to the Agency. Second, interviewees should be recruited so as to provide an unbiased and representative sample of the target population. We note that in this case the interviewees appear to be a convenience sample of cardiologists affiliated with the Applicant but not directly involved in the VOYAGER PAD program. This does not necessarily invalidate their perspectives but does increase the potential for bias and non-representativeness. Third, interview notes and transcripts should be submitted to the Agency for review in addition to a summary of numerical responses. This qualitative information is crucial for reviewing and interpreting the numeric findings. Finally, we note that FDA PFDD Guidance provides general considerations on the design and execution of interview studies that may be relevant.

After reviewing the EQ-5D data the Applicant concluded that significant missing data precluded its use (Seq 0433; May 27, 2021). DSAS generally agrees with this assessment. A planned PFDD Guidance on incorporating clinical outcome assessments into endpoints for regulatory decision making (FDA 2019) may include recommendations useful to Sponsors when incorporating instruments like the EQ-5D (which is a type of clinical outcome assessment and patient reported

outcome) into clinical trials. Earlier guidance from CDRH (FDA 2009) provides advice to sponsors on the use of patient reported outcomes into development programs; this guidance may also be helpful for Sponsors. We also note that the ISPOR Good Research Practices Task Force provides recommendations on collecting data for HSUVs as part of the pivotal clinical trial (Wolowacz, 2016). Issues to consider that may have been particularly relevant in the rivaroxaban for PAD trial include: the timing of assessments relative to events; the total number of assessments that will be required; representativeness of the trial population for the target (and in FDA's case, US) population; and anticipation of missing data and plans for adjustment.

b. Follow-up time for subjects without listed clinical events

In the Applicant's Global Rank and Win Ratio (Dong Method) analyses, event timing is considered in ranking but only for those events listed in the hierarchy rankings.

For Global Rank, all subjects without events were assigned the best, and equal, rank, regardless of censoring or follow-up time. The Applicant noted (Seq 0442; June 25, 2021) that the literature references do not specify inclusion of follow-up time for subjects without events.

However, in the Applicant's referenced literature (Subherwal 2012), it is stated that an acceptable follow-up time is required for the Global Rank method. The Applicant did not utilize follow-up thresholds for subject inclusion in the analysis; utilization of a follow-up threshold which could be supportive of the exclusion of time for subjects with no events.

For the Win Ratio (Dong Method), the Applicant did not include follow-up time when both subjects did not have events, again citing literature (Pocock 2012) (Seq 0442; June 25, 2021).

Based on the referenced literature, two methods of pairwise formation are described: 1) matched and unmatched:

- The matched pairs approach considers subject risk and develops a methodology to match subjects in the treatment and placebo groups for comparison
- The unmatched pairs approach uses all pairwise combinations

The applicant notes the literature states that subjects without events should be tied; however, the author only provides this statement when using the matched approach; no similar description is provided for the unmatched approach. Given the unmatched approach does not consider subject risk profile, follow-up time could provide useful in differentiating treatment and placebo.

In addition, Pocock has noted further research is warranted in the use of follow-up time for subjects without clinical events of interest to assess the "magnitude of the win".

Therefore, based on the Applicant's selected utilization of these methods, DSAS has determined that further analysis should be conducted to quantify the impact of: 1) selecting a threshold or follow-up minimum for inclusion in analysis based on accepted standards (Global Rank only) and 2) using follow-up time as a tiebreaker for subjects without events. We note that option 2 was employed as a sensitivity analysis for the ordinal DOOR approach.

XI. Summary

a. Conclusions for Rivaroxaban for PAD

The review team for the supplemental NDA for rivaroxaban for PAD undertook a formal benefit-risk assessment to assess the sensitivity of the benefit-risk balance to different assumptions about tradeoffs between outcomes, changes in the incidence of outcomes over time, and to the statistical uncertainty in the incidence of outcomes. When considering FDA-supplied tradeoffs between outcomes and the results of the VOYAGER PAD trial, the analyses do not clearly favor rivaroxaban over placebo. The results do more strongly favor rivaroxaban when all-cause mortality event rates are adjusted to reflect stated beliefs, and prior evidence, about the true effect of rivaroxaban on all-cause mortality. This conclusion is sensitive to weights placed on key outcomes and to beliefs about the true effect of rivaroxaban on mortality.

At the Review Team's suggestion, the Applicant for rivaroxaban also submitted their own analyses which show that rivaroxaban has a favorable benefit-risk profile. However, the outcome hierarchies and weights assumed by the Applicant differ from the stated tradeoffs given by FDA. Reconciling differences in tradeoffs is challenging.

b. Future areas of exploration

The experience of rivaroxaban for PAD provided methodological and process learnings:

1. A mortality imbalance, even a small one, will strongly influence MCDA results. Therefore, it is important to articulate beliefs about that imbalance before modeling.
2. Advantages and disadvantages of survey versus interview mechanisms for collecting tradeoff information. Surveys allow for input from more individuals but are challenging to construct and interviews may allow for deeper understanding.
3. Consistency of conclusions between group-level (MCDA and wNCB) and patient-level (win ratio, global rank, and DOOR) methodologies for contexts with relatively rare outcomes.

The experience also led to a number of methodological and process questions for the Center to consider. Areas for future exploration include:

1. Clarifying the situations where additional analyses may be most valuable to inform regulatory decision making.
2. Articulating in what contexts the Agency should communicate to the Applicant that the Agency is conducting additional benefit-risk analyses as part of its review. When should the Agency recommend or request that the Applicant conduct their own in parallel? What guidance should the Agency provide for the source of weights?
3. Conducting additional "side-by-side" comparisons of multiple methods to determine when use of multiple methods add value and to better understand the appropriate context of use for each method. Using more than one method increases confidence but also increases the time required to complete the analysis, review any analysis conducted by the Applicant, and evaluate the results.
4. Identify opportunities to conduct additional test cases that address:
    a. Pre-specification of weights: identify a suitable case and specify review team tradeoffs and weights before results of the pivotal trial are available.
    b. Patient preferences as a source of weights: conduct a case that utilizes both review team and patient preferences.

    c. Outcomes: evaluate the methods for benefit-risk assessments with non-event outcomes and other outcomes that are more challenging to compare than the ones in the case of Rivaroxaban for PAD.
    d. Level of evidence: evaluate the methods for Applications relying on smaller trials, trials with external controls, and real-world evidence.
5. Refine visualization and communication approaches in order to communicate model results completely but succinctly for FDA decision-makers.
6. Development of CDER best practices for specification of review team weights and tradeoffs. Consideration of a survey-based mechanism that can quickly be deployed to a large sample of clinicians with appropriate expertise.
7. Investigate methodologies for potentially communicating results to patients and physicians to support individual benefit-risk assessments and decision-making. Further assessment would be needed to determine appropriateness of any such communication.
8. Consideration of if, how, and when, information external to the pivotal trial should be incorporated into analyses. Technical solutions, such as meta-analysis, are available but there may be disagreement about the appropriateness of such approaches for specific contexts.
9. Specification of the appropriate decision-making perspective, if using regulator preferences. Should benefit-risk analysis results be interpreted from the perspective of a single decision-maker or a group? If group models are considered, how should differences between individuals be handled?

XII. References

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XIII. Appendix

Table A1. Available baseline characteristics potentially indicative of the severity of subsequent nonfatal events

Outcome	Baseline characteristics	Percent of events
Myocardial infarction	History of coronary artery disease	51%
	History of heart failure	10%
	History of myocardial infarction	27%
	History of carotid artery disease	15%
Acute limb ischemia	Critical limb ischemia (history or ongoing)	38%
	Major or minor ischemic amputation (history)	4%
Major amputation of vascular etiology	Critical limb ischemia (history or ongoing)	59%
	Major or minor ischemic amputation (history)	20%

Table A2. Available event characteristics potentially indicative of the severity of the non-fatal event

Outcome	Event characteristics	Percent of events
Myocardial infarction	Type 1 (spontaneous)	62%
	Type 2 (ischemic imbalance)	32%
	Type 3	0%
	Type 4a (PCI related)	3%
	Type 4b (stent thrombosis)	1%
	Type 4c (stent restenosis)	1%
	Type 5 (CABG related)	1%
Major amputation of vascular etiology	Lower extremity amputation	100%
	Index leg amputation	83%
	Above ankle amputation	100%
TIMI intracranial bleed	Symptomatic bleeding of a critical area or organ	97%
	Bleeding causing a fall in HB of >=2 g/dL (or HCT >=6%) or leading to transfusion of >=2 units of whole blood or red blood cells	10%

		Non-intracranial major	Minor	Requiring medical attention	Minimal
Other TIMI bleeds	The subject was hospitalized	10%	6%	2%	0%
	Symptomatic bleeding of a critical area or organ	12%	6%	5%	0%
	Bleeding causing a fall in HB of >=2 g/dL (or HCT >=6%) or leading to transfusion of >=2 units of whole blood or red blood cells	100%	100%	13%	2%
	Gastrointestinal tract bleeding	57%	47%	7%	0%
	Requires medical attention (e.g., hospitalization, medical treatment for bleeding)	2%	0%	0%	0%
	Required an unplanned take back procedure to control bleeding	21%	18%	5%	0%
	Bleeding related to the index revascularization procedure	4%	9%	1%	0%
	Transfusion of 2 or more units of packed red blood cells or whole blood	19%	6%	19%	0%

Figure A1. Mean change in visual analogue scale (VAS). For each event, the change is the difference between the VAS response immediately preceding the event and the VAS response immediately preceding the event (time limited to no more than 8 months between the questionnaire and the event, based on the frequency of questionnaire administration in VOYAGER PAD). Observations were excluded if more than one outcome type occurred between questionnaires. Orange bars represent the mean change in VAS among subjects with VAS responses at both timepoints (pre and post). Grey bars represent the mean change in VAS for all subjects with VAS responses prior to the event; in this case, missing post-event responses are assumed to be zero under the assumption that missing responses are due to a poor health status. The true change in VAS likely falls between the grey and orange bar. Also shown for context is the average change in VAS between questionnaire administrations for all subjects who did not experience any events. Of note, revascularization is associated with an increase in the VAS. This is likely because a revascularization procedure is performed in order to improve pain, function, and quality of live. The outcome of interest for the MCDA is not the revascularization procedure itself but rather the precipitating need for revascularization.

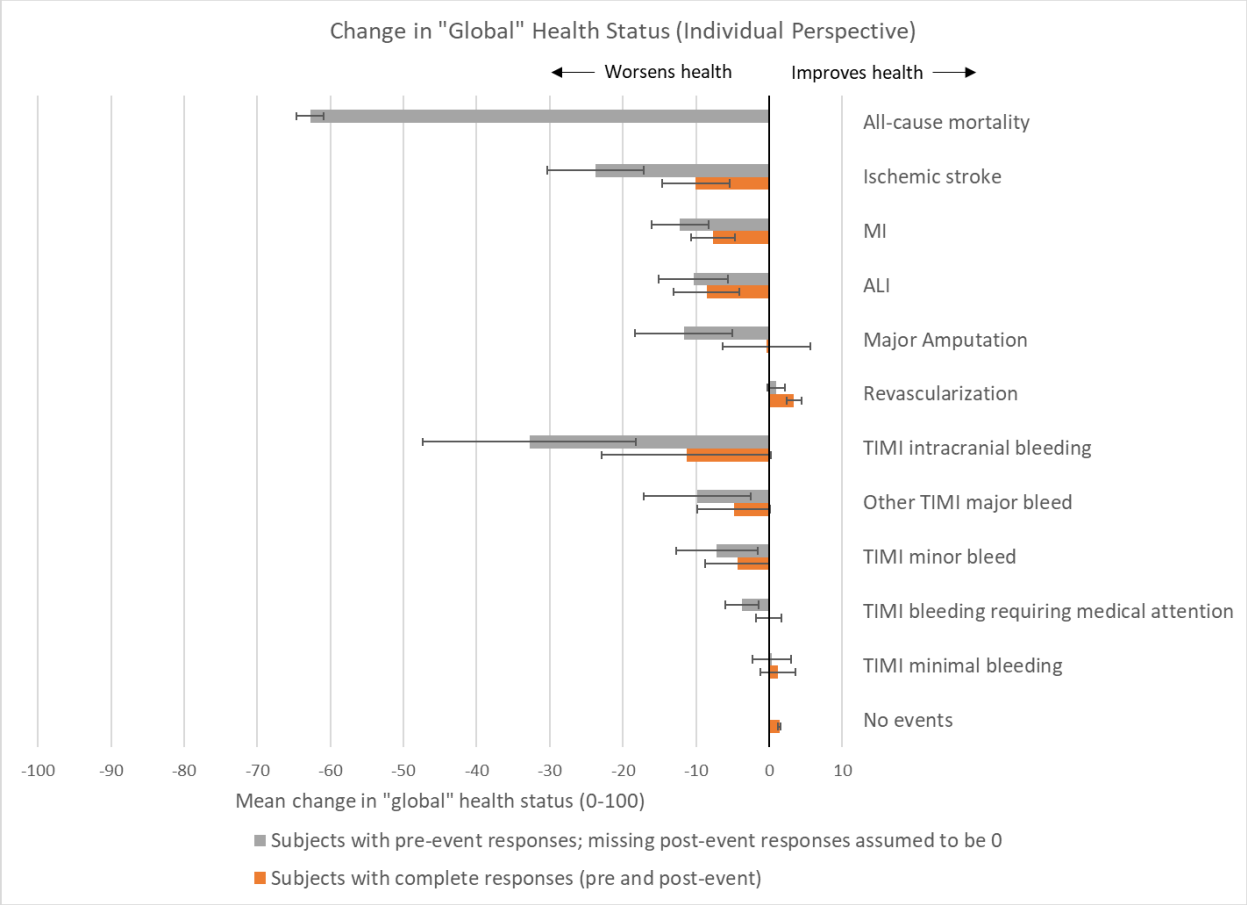

Table A3. Example MCDA calculation.

Outcome	Best-Plausible	Worst-Plausible	Tradeoff	Swing Weight	Weight	Performance option	Normalized Performance	Score
Outcome 1 ("key" outcome)	$R_{Best, Key}$	$R_{Worst, Key}$	T_{Key}	$SW_{Key} = 100 * [(R_{Worst, Key} - R_{Best, Key}) / (R_{Worst, Key} - R_{Best, Key})] * [T_{Key}/T_{Key}]$	$W_{Key} = SW_{Key} / SUM_{SW}$	P_{Key}	$NP_{Key} = (R_{Worst, Key}-P_{Key}) / (R_{Worst, Key}- R_{Best, Key})$	$S_{Key} = W_{Key}* NP_{Key}$
Outcome 2	$R_{Best, O2}$	$R_{Worst, O2}$	T_{O2}	$SW_{O2} = 100 * [(R_{Worst, O2} - R_{Best, O2}) / (R_{Worst, Key} - R_{Best, Key})] * [T_{Key}/T_{O2}]$	$W_{O2} = SW_{Key} / SUM_{SW}$	P_{O2}	$NP_{O2} = (R_{Worst, O2}-P_{O2}) / (R_{Worst, O2}- R_{Best, O2})$	$S_{O2} = W_{O2}* NP_{O2}$
Outcome 3	$R_{Best, O3}$	$R_{Worst, O3}$	T_{O3}	$SW_{O3} = 100 * [(R_{Worst, O3} - R_{Best, O3}) / (R_{Worst, Key} - R_{Best, Key})] * [T_{Key}/T_{O3}]$	$W_{O3} = SW_{Key} / SUM_{SW}$	P_{O3}	$NP_{O3} = (R_{Worst, O3}-P_{O3}) / (R_{Worst, O3}- R_{Best, O3})$	$S_{O3} = W_{O3}* NP_{O3}$
Total				$SUM_{SW} = SW_{Key} + SW_{O2} + SW_{O3}$	$W_{Key} + W_{O2} + W_{O3} = 1$			$S_{Total} = V_{Key}+ V_{O2} + V_{O3}$

Table A4. Literature HSUVs identified by DSAS from Applicant's submission. The Applicant's initial search identified 373 potentially-relevant HSUVs. DSAS applied our proposed algorithm, based on the ISPOR good practices report (Brazier, 2019), to this list to identify the most relevant HSUVs:

1. Of the 373, 161 were measured in patients using EQ-5D.
2. Of the 161, 41 were excluded because of one or more of the following:
    a. the Applicant found insufficient data to determine if the population "closely" or "broadly" approximated the VOYAGER PAD population;
    b. the Applicant found insufficient data to determine if the outcomes "closely" or "broadly" approximated the VOYAGER PAD outcomes;
    c. the study was conducted outside the US, Canada, or Europe or the country was unknown; or
    d. sample size was <20 subjects.
3. Of the remaining 120, 8 were excluded because of two or more of the following:
    a. the applicant considered the population to "broadly" (not "closely") approximate the VOYAGER PAD population;
    b. the Applicant considered the outcomes to "broadly" (not "closely") approximate the VOYAGER PAD outcomes;
    c. the study was conducted in multiple countries; or
    d. sample size was not stated.
4. Of the remaining 112, 68 HSUVs were excluded because a better estimate or timepoint was available from the same reference.
5. Of the remaining 44, 26 references reported a single HSUV, and 8 references reported 18 HSUVs (e.g., HSUVs were reported separately for men and women). So as to not over-weight the 18 relative to the 26, the 18 were averaged within their reference to produce a single HSUV for each reference.

The result of the DSAS-proposed algorithm is 34 HSUVs.

Outcome	Reference	Notes on inclusion	Average of	Timepoint	HSUV
Non-fatal ischemic stroke	Vaidya, 2014	--	--	NA	0.45
	Itoga, 2018	Population "broadly" matches	--	1-month	0.64
	Stam-Slob, 2017	Population "broadly" matches	--	NA	0.69
	Pietzsch, 2019	Outcome "broadly" matches	--	12-months	0.72
	Grima, 2014	--	Treatment arm (2)	Permanent	0.73
	Theidel, 2013	--	Treatment arm (2)	NA	0.73
	Cowie, 2020	--	--	Post-acute	0.74
	Janzon, 2015	Multiple countries	Treatment arm (2)	12-months	0.74
Non-fatal myocardial infarction	Pietzsch, 2019	--	--	12-months	0.43
	Dewilde, 2012	--	--	Post-acute	0.63
	Kourlaba, 2014	Population "broadly" matches	--	6-weeks	0.68
	Soto, 2016	Population "broadly" matches	--	3-months	0.69
	Chan, 2016	Population "broadly" matches	--	12-months	0.70
	Jones, 2019	Sample size not stated	--	NA	0.70
	Almekhlafi 2014	Outcome "broadly" matches	Sex subgroups (2)	12-months	0.74
	Janzon, 2015	Sample size not stated	--	12-months	0.77
	Cowie, 2020	--	--	Post-acute	0.81
	Ying, 2016	Population "broadly" matches	--	12-months	0.83
	Kourlaba, 2012	--	--	12-months	0.93
	Gouveia, 2015	--	--	NA	0.94
	Nikolic, 2013	--	--	12-months	0.94
	Moriarty, 2019	Population "broadly" matches	--	12-months	0.95
Non-fatal acute limb ischemia	Spronk, 2008	Outcome "broadly" matches	--	12-months	0.11
	de Vries, 2002	Population "broadly" matches	--	NA	0.45

	Forbes, 2010	--	Treatment arm (2)	12-months	0.56
	Sigvant, 2011	6-month timepoint	--	6-months	0.68
	Bermingham, 2013	Outcome “broadly” matches	Subgroup-by-treatment (2x2)	12-months	0.72
	Salisbury, 2016	Population “broadly” matches	Treatment arm (2)	12-months	0.81
	Villemoes, 2018	Population “broadly” matches	--	12-months	0.85
Non-fatal major amputation	Oostenbrink, 2001	--	Sex subgroup (2)	21-months	0.47
	Villemoes, 2018	Multiple countries	--	Not stated	0.88
Non-fatal major intracranial bleeding	Kim, 2019	Multiple countries	--	3-months	0.62
	Cowie, 2020	--	--	Post-acute	0.76
Non-fatal major non-intracranial bleeding	Cowie, 2020	Multiple countries	--	3-months	0.98

Table A5: Global Rank Method Description

$$U_T = n_T * n_P + \frac{n_T * (n_T + 1)}{2} - R_T$$

$$U_P = n_T * n_P + \frac{n_P * (n_P + 1)}{2} - R_P$$

Where R_T and R_P are the sum of the ranks for treatment and placebo, respectively, and n_T and n_P are the number of subjects in the treatment and placebo groups, respectively

Van Elteren test for differences: An extension of the Wilcoxon-Mann-Whitney sum rank test for stratified data

Table A6: Win Ratio Method as described by Dong

$$Win\ Ratio = \frac{N_W}{N_L}$$

Where: N_W = "Winners" in the treatment group; and
N_L = "Losers" in the treatment group

Table A7. Win Ratio Follmann Method Description. The Follmann method creates ordering scores, O, which take into account both event time and event severity over discrete follow-up intervals like is done with multiple interval censoring. Subjects are included in each interval until they either have an event or are censored. Cox PH regression can be fit, including additional covariates in the analysis, and the hazard ratio is interpreted as the Win Ratio

Ordering Score O	$O = T_A + (1-E_A)E_B(\tau + T_B) + (1-E_A)(1-E_B)E_C(2\tau + T_C) +$ $(1-E_A)(1-E_B)(1-E_C)E_D(3\tau + T_D) +$ $(1-E_A)(1-E_B)(1-E_C)(1-E_D)E_E(4\tau + T_E) +$ $(1-E_A)(1-E_B)(1-E_C)(1-E_D)(1-E_E)E_F(5\tau + T_F) + (1-E_A)(1-E_B$ $)(1-E_C)(1-E_D)(1-E_E)(1-E_F)E_G(6\tau + T_G) + (1-E_A)(1-E_B)(1-E_C$ $)(1-E_D)(1-E_E)(1-E_F)(1-E_G)(7\tau)$ where T_i is the time to event *i* in event (A, B, C, D, E, F, G) and E_i in (1,0) is the event indicator and τ is the maximal observed time over the entire study

Table A8. Description of the Ordinal DOOR Method.

DOOR Probability = $\frac{N_W + 0.5 * T_T}{N_T * N_P}$

DOOR Net Benefit = $\frac{N_W - N_L}{N_T * N_P}$

Where: $N_W = Number\ of\ Winners\ in\ the\ treatment\ group$
$N_L = Number\ of\ Losers\ in\ the\ treatment\ group$
$T_T = Number\ of\ Ties\ in\ the\ treatment\ group$
$N_T = Number\ of\ subjects\ in\ the\ treatment\ group$
$N_P = Number\ of\ subjects\ in\ the\ placebo\ group$

Table A9. Description of the Weighted DOOR Method

$$\overline{W_i} = \frac{\sum_{j=1}^{N_i} W_{ij}}{N_i}$$

where W_{ij} is the partial credit for subject j in arm i, j = 1,...,N_i
The difference in mean partial credit between arms is:

$$\boldsymbol{WD} = \overline{\boldsymbol{W_T}} - \overline{\boldsymbol{W_P}}$$

where $\overline{W_T}$ and $\overline{W_P}$ are the mean partial credit for the treatment and placebo groups, respectively

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/s/

LEILA G LACKEY
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202439Orig1s035

PRODUCT QUALITY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number: NDA 202439 / S-035**

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original	PAS (Efficacy)	10/23/2020	10/23/2020	8/9/2021	4/23/2021	8/16/2021

3. **Provides For:** inclusion of a new proposed indication to reduce the risk of major thrombotic vascular events in patients after lower extremity revascularization due to symptomatic peripheral artery disease (PAD) in the prescribing information.

4. **Review #:** 1

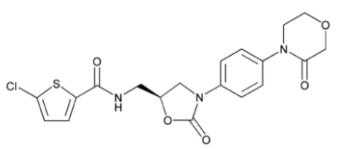
5. **Clinical Review Division:** CDER/OCHEN/DCN

6. **Name and Address of Applicant**:
   Janssen Pharmaceuticals, Inc.
   1125 Trenton-Harbourton Road
   Titusville, New Jersey 08560

7. **Drug Product**:

Drug Name	Dosage Form	Strengths	Route of Administration	Rx or OTC	Special Product
Xarelto® (rivaroxaban) tablets	Tablets	2.5 mg, 15 mg, 10 mg, and 20 mg	Oral	Rx	No

8. **Chemical Name and Structure of Drug Substance**:

	**USAN:** Rivaroxaban **CAS Number:** 366789-02-8 **Chemical name:** 5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide **Molecular formula**: $C_{19}H_{18}ClN_3O_5S$ **MW:** 435.88 g/mol

9. **Indication**: for the reduction in the risk of stroke and systemic embolism in nonvalvular atrial fibrillation. Also, for the treatment of deep vein thrombosis (DVT), for treatment of pulmonary embolism (PE), for reduction in the risk of recurrence of DVT or PE, for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery, for prophylaxis of venous thromboembolism (VTE) in acutely ill medical patients, and to reduce the risk of major cardiovascular events in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD).

10. Supporting/Relating Documents: See pages 4-5.

11. Consults: None

12. Executive Summary:

OND Managed: In this supplemental submission, the applicant proposes to extend the use of Xarelto® (rivaroxaban) tablets to include reducing the risk of major thrombotic vascular events in patients after lower extremity revascularization due to symptomatic peripheral artery disease (PAD).

No changes have been made to the CMC sections of the application and the applicant has provided a categorical exclusion for Environmental Assessment. The applicant claims categorical exclusion under 21 CFR 25.31(b) from the requirement to prepare an Environmental Assessment because approval of this supplemental submission will not increase the estimated concentration of the drug substance at the point of entry into the aquatic environment above 1 part per billion. Based upon the calculations provided (see details in the body of the review), the claim of categorical exclusion appears to be warranted.

The submitted draft "United States Prescribing Information" (USPI) (annotated, tracked-changes) showed no changes to the currently approved CMC-related information included in Section "2 DOSAGE AND ADMINISTRATION". The submitted draft "USPI" (annotated, tracked-changes) showed no changes at all to Sections "3 DOSAGE FORMS AND STRENGTHS", and "11 DESCRIPTION"; all CMC-related information proposes no changes to the currently approved. In Section "16 HOW SUPPLIED/STORAGE AND HANDLING", the statement describing the prescribed storage conditions for the Xarelto Tablets was updated. The current statement, namely "Store at 25°C (77°F) or room temperature; excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]", was updated to read as "Store at room temperature between 20°C to 25°C (68°F to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]". The rationale given for the change from a single number, namely 25°C (77°F), to a range, namely 20°C to 25°C (68°F to 77°F), was to make the storage information in the "USPI" consistent with that in the Medication Guide. As per "USP <659> Packaging and Storage Requirements", the term "controlled room temperature" is defined as "the temperature maintained thermostatically that encompasses the usual and customary working environment of 20°–25°[C] (68°–77°F)." Hence, the proposed change to the storage statement is deemed acceptable from a CMC perspective.

13. Conclusions & Recommendations:

This supplemental submission is recommended for approval from a CMC standpoint.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:

Richard T. Matsuoka, Ph.D., CMC reviewer, Branch 3, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:

Gurpreet Gill-Sangha, Ph.D., Branch Chief, Branch 3, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

CMC ASSESSMENT

I BACKGROUND INFORMATION

Xarelto® (rivaroxaban) tablets, approved on 11/04/2011, contain either 2.5 mg, 10 mg, 15 mg, or 20 mg of rivaroxaban drug substance. The tablets also contain the following inactive ingredients: "croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate".
As per "USP <659> Packaging and Storage Requirements" and pertinent to this review, the term "controlled room temperature" is defined as "the temperature maintained thermostatically that encompasses the usual and customary working environment of 20°-25°[C] (68°–77°F)." Moreover, mean kinetic temperature (MKT) maybe used during an excursion provided: "1) MKT does not exceed 25°[C] (77°F); 2) excursion between 15° and 30°[C] (59° and 86°F); 3) transient excursions are NMT 40°[C] (104° F); and 4) excursion time is NMT 24 h. These limits (time and temperature) and the calculated MKT must be documented."

II PROPOSED CHANGES

The applicant proposes to extend the use of Xarelto® (rivaroxaban) tablets to include reducing the risk of major thrombotic vascular events in patients after lower extremity revascularization due to symptomatic peripheral artery disease (PAD).

III DATA SUBMITTED TO SUPPORT THE PROPOSED CHANGES

1. OTHER CORRESPONDENCE (1.12)

A. Environmental Analysis (1.12.14)

Comments: The applicant claims categorical exclusion from the requirement to prepare an Environmental Assessment for this supplemental submission because approval of this action would result in a concentration of the active moiety (rivaroxaban) in the aquatic environment of the United States below 1 part per billion (ppb); this claim is in accordance with the categorical exclusion criteria of 21 CFR 25.31(b). More specifically, the applicant states that this claim is based on a maximum yearly usage estimate for the drug substance of (b) (4) using 5-year forecast information for all formulations. Based on this estimate, the expected introduction concentration (EIC) of the active moiety into the aquatic environment is (b) (4) Moreover, the applicant certifies that, to the best of their knowledge, "no extraordinary circumstances exit" where the proposed action may significantly affect the quality of the human environment.

☑ **Reviewer Evaluation: Acceptable**

2. LABELING (1.14)

A. Draft Labeling (1.14.1)

A(i) Annotated Draft Labeling Text (1.14.1.2)

Comments: The submitted draft "United States Prescribing Information" (USPI) (annotated, tracked-changes) showed no changes to the CMC-related information included in Section "2 DOSAGE AND ADMINISTRATION". The submitted draft "USPI" (annotated, tracked-changes) showed no changes at all to Sections "3 DOSAGE FORMS AND STRENGTHS", and "11 DESCRIPTION"; all CMC-related information is the same as the currently approved.

In Section "16 HOW SUPPLIED/STORAGE AND HANDLING", the statement describing the prescribed storage conditions for the Xarelto Tablets were updated. The current statement, namely "Store at 25°C (77°F) or room temperature; excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]", was updated to read as "Store at room temperature between 20°C to 25°C (68°F to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]" (see screen shot below). As noted in Footnote Number 48 (see screen shot of footnote below), the rationale for the change from a single number, namely 25°C (77°F), to a range, namely 20°C to 25°C (68°F to 77°F), was to make the storage information in the "USPI" consistent with that in the Medication Guide. As per "USP <659> Packaging and Storage Requirements", the term "controlled room temperature" is defined as "the temperature maintained thermostatically that encompasses the usual and customary working environment of 20°–25°[C] (68°-77°F)." Hence, the proposed change to the storage statement is deemed acceptable from a CMC perspective. As noted by the applicant, the change from the hyphen "-" to the word "to" between temperature ranges was an editorial revision.

☑ **Reviewer Evaluation: Acceptable**

Store at room temperature between 20°C to 25°C (68°F to 77°F) ~~or room temperature~~; excursions permitted to 15°C ~~–~~ to 30°C (59°F ~~-~~ to 86°F) [see USP Controlled Room Temperature].[48]

[48] Rationale: Modified for consistency with Medication Guide and included additional editorial revision to change from "–" to "to" between temperature ranges.

IV RISK ASSOCIATED WITH THE PROPOSED CHANGES AND IMPACT TO PRODUCT QUALITY AND PATIENT SAFETY

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Richard Matsuoka

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Gurpreet Gill Sangha

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BRIDGET E KANE
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202439Orig1s035

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 13, 2021

To: Bridget Kane, Regulatory Health Project Manager
Division of Cardiovascular and Renal Products (DCRP)

Michael Monteleone, Associate Director for Labeling, (DCRP)

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for Xarelto (rivaroxaban) Tablets

NDA: 202439/Supplement 035

In response to DCRP consult request dated December 16, 2020, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for Xarelto (rivaroxaban) Tablets. This supplement (S035) supports inclusion of a new proposed indication to reduce the risk of major thrombotic vascular events in patients after lower extremity revascularization due to symptomatic peripheral artery disease (PAD) in the prescribing information.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DCRP on June 30, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed were sent under separate cover on July 1, 2021.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov

58 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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DAVID F FOSS
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	July 1, 2021
To:	Bridget Kane, MS Regulatory Project Manager **Division of Cardiology and Nephrology (DCN)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Concurrence with Submitted: Medication Guide (MG)
Drug Name (established name):	XARELTO (rivaroxaban)
Dosage Form and Route:	Tablets, for oral use
Application Type/Number:	NDA 202439
Supplement Number:	S-035
Applicant:	Janssen Research & Development, LLC

1 INTRODUCTION

On October 23, 2020, Janssen Research & Development, LLC submitted for the Agency's review a Prior Approval Supplement-Efficacy (PAS-035) to their original New Drug Application (NDA-202439) for XARELTO (rivaroxaban) 2.5 mg immediate release tablets to support inclusion of a new proposed indication to reduce the risk of major thrombotic vascular events in patients after lower extremity revascularization due to symptomatic peripheral artery disease (PAD) in the prescribing information. On December 15, 2020, the Division of Cardiology and Nephrology (DCN) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for XARELTO (rivaroxaban) tablets, for oral use.

This memorandum documents the DMPP review and concurrence with the Applicant's proposed MG for XARELTO (rivaroxaban) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft XARELTO (rivaroxaban) MG received on October 23, 2020, and received by DMPP on June 30, 2021.
- Draft XARELTO (rivaroxaban) Prescribing Information (PI) received on October 23, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on June 30, 2021.
- TRADENAME XARELTO (rivaroxaban) MG approved January 28, 2021.

3 CONCLUSIONS

We find the Applicant's proposed MG is acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 25, 2021
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 202439/S-035
Product Name, Dosage Form, and Strength:	Xarelto (Rivaroxaban) tablets, 2.5 mg, 10 mg, 15 mg, 20 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Janssen Pharmaceuticals, Inc.
FDA Received Date:	October 23, 2020 and February 9, 2021
OSE RCM #:	2020-2248
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Janssen Pharmaceuticals, Inc. submitted a supplemental New Drug Application (sNDA) for NDA 202439/S-035 for Xarelto (Rivaroxaban) tablets proposing a new indication to reduce the risk of major thrombotic vascular events in patients after lower extremity revascularization due to symptomatic peripheral artery disease (PAD).

We reviewed the proposed updated Xarelto Prescribing Information (PI) and medication guide for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Xarelto (Rivaroxaban) tablets approved on November 4, 2011 is a factor Xa inhibitor indicated:

- To reduce risk of stroke and systemic embolism in nonvalvular atrial fibrillation
- For treatment of deep vein thrombosis (DVT)
- For treatment of pulmonary embolism (PE)
- For reduction in the risk of recurrence of DVT or PE
- For the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery
- For prophylaxis of venous thromboembolism (VTE) in acutely ill medical patients
- To reduce the risk of major cardiovascular events in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD)

It is available as 2.5 mg, 10 mg, 15 mg and 20 mg tablets.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Janssen Pharmaceuticals, Inc. submitted a supplemental New Drug Application (sNDA) for NDA 202439/S-035 for Xarelto (Rivaroxaban) tablets proposing a new indication to reduce the risk of major thrombotic vascular events in patients after lower extremity revascularization due to symptomatic peripheral artery disease (PAD) in the prescribing information.

We performed a risk assessment of the proposed PI and Medication Guide to determine if they are acceptable from a medication error perspective. We note the starting dose for the indication to reduce the risk of major thrombotic vascular events in patients after lower extremity revascularization due to symptomatic PAD is the same (2.5 mg twice daily) as that for the indication of reduction of risk of major cardiovascular events in chronic CAD or PAD.

We note that the temperature statement has been changed in the PI from "Store at 25° C (77° F) or room temperature; excursions permitted to 15°-30° C (59°-86° F) [see USP Controlled Room Temperature]." to "Store at room temperature between 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]." As such the container labels, carton labeling, and Medication Guide need to be updated with the revised storage information. We provide recommendation below for the Division for the Medication Guide and the Applicant to revise and submit updated carton and container labeling.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI is acceptable from a medication error perspective. We provide recommendation below for the Division for the Medication Guide and the Applicant to revise and submit updated carton and container labeling.

4.1 RECOMMENDATION FOR THE DIVISION

A. Medication Guide

1. We note the update to the storage information in Section 16 of the Prescribing Information (PI). We recommend the storage statement be revised to "Store Xarelto at room temperature between 68°F to 77°F (20°C to 25°C)." to align with the PI.

4.2 RECOMMENDATIONS FOR JANSSEN PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA Supplement:

A. General Comments (Container Labels and Carton Labeling)

1. We note the update to the storage information in Section 16 of the Prescribing Information. We recommend you revise the storage statement on the carton labeling and container labels to "Store at room temperature between 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]." so that it aligns with the PI.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xarelto received on October 23, 2020 from Janssen Pharmaceuticals, Inc..

Table 2. Relevant Product Information for Xarelto

Initial Approval Date	November 4, 2011
Active Ingredient	Rivaroxaban
Indication	Xarelto (Rivaroxaban) tablets approved on November 4, 2011 is a factor Xa inhibitor indicated: • To reduce risk of stroke and systemic embolism in nonvalvular atrial fibrillation • For treatment of deep vein thrombosis (DVT) • For treatment of pulmonary embolism (PE) • For reduction in the risk of recurrence of DVT or PE • For the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery • For prophylaxis of venous thromboembolism (VTE) in acutely ill medical patients • To reduce the risk of major cardiovascular events in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD) **Proposed:** • To reduce the risk of major thrombotic vascular events in patients after recent lower extremity revascularization due to symptomatic PAD
Route of Administration	Oral
Dosage Form	tablets
Strength	2.5 mg, 10 mg, 15 mg, 20 mg
Dose and Frequency	See nested table below

Indication	**Renal Considerations***	**Dosage**	**Food/Timing†**
Reduction in Risk of Stroke in Nonvalvular Atrial Fibrillation	CrCl >50 mL/min	20 mg once daily	Take with evening meal
	CrCl ≤50 mL/min	15 mg once daily	Take with evening meal
Treatment of DVT and/or PE	CrCl ≥15 mL/min	15 mg twice daily ▼ **after 21 days, transition to** ▼ 20 mg once daily	Take with food, at the same time each day
	CrCl <15 mL/min	Avoid Use	

	Reduction in the Risk of Recurrence of DVT and/or PE in patients at continued risk for DVT and/or PE	CrCl ≥15 mL/min	10 mg once daily, after at least 6 months of standard anticoagulant treatment	Take with or without food
		CrCl <15 mL/min	Avoid Use	
	Prophylaxis of DVT Following:			
	- Hip Replacement Surgery‡	CrCl ≥15 mL/min	10 mg once daily for 35 days, 6-10 hours after surgery once hemostasis has been established	Take with or without food
		CrCl <15 mL/min	Avoid Use	
	- Knee Replacement Surgery‡	CrCl ≥15 mL/min	10 mg once daily for 12 days, 6-10 hours after surgery once hemostasis has been established	Take with or without food
		CrCl <15 mL/min	Avoid Use	
	Reduction of Risk of Major Cardiovascular Events (CV Death, MI, and Stroke) in Chronic CAD or PAD	No dose adjustment needed based on CrCl	2.5 mg twice daily, plus aspirin (75-100 mg) once daily	Take with or without food
	Proposed:			
	Reduction of Risk of Major Thrombotic Vascular Events After Lower Extremity Revascularization due to Symptomatic PAD	No dose adjustment needed based on CrCl	2.5 mg twice daily, plus aspirin (75-100 mg) once daily, initiated after a successful lower extremity revascularization procedure once hemostasis has been established	Take with or without food
How Supplied	• 2.5 mg tablets are round, light yellow, and film-coated with a triangle pointing down above a "2.5" marked on one side and "Xa" on the other side. The tablets are supplied in the packages listed: NDC 50458-577-60 Bottle containing 60 tablets NDC 50458-577-18 Bottle containing 180 tablets NDC 50458-577-10 Blister package containing 100 tablets (10 blister cards containing 10 tablets each)			

	• 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 50458-580-90 Bottle containing 90 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 50458-579-89 Bulk bottle containing 1000 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
Storage	“Store at room temperature between 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 15, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, “Xarelto”, “rivaroxaban” and “NDA 202439”. Our search identified 2[a,b] previous reviews and we considered our previous recommendations to see if they are applicable for this current review.

[a] DeGraw, S. Label and Labeling Review for Xarelto (NDA 022406/S-027). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 10. RCM No.: 2018-1293-1.

[b] Garrison, N. Label and Labeling Review for Xarelto (NDA 022406/S-034). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUN 13. RCM No.: 2019-510.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Xarelto labels and labeling submitted by Janssen Pharmaceuticals, Inc.

- Prescribing Information and Medication Guide (Image not shown) received on October 23, 2020, available from:
  - Clean: \\CDSESUB1\evsprod\nda202439\0385\m1\us\clean-draft-labeling-text-voyager.doc
  - Tracked: \\CDSESUB1\evsprod\nda202439\0385\m1\us\marked-draft-labeling-text-voyager.doc

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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MAXIMILIAN STRAKA
03/25/2021 11:20:39 AM

HINA S MEHTA
03/25/2021 11:32:37 AM