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Landmark Phase 3 VOYAGER PAD Study of XARELTO® (rivaroxaban) Plus Aspirin Shows Significant Benefit in Patients with Symptomatic Peripheral Artery Disease (PAD) after Lower-Extremity Revascularization

XARELTO® has the potential to be the first anticoagulant in 20 years[i] to show a benefit in these high-risk patients

Two major Phase 3 trials have evaluated XARELTO® vascular dose plus aspirin in treating patients with atherosclerotic disease

RARITAN, NJ, March 28, 2020 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced the VOYAGER PAD study met its primary efficacy and principal safety endpoints, demonstrating the XARELTO® (rivaroxaban) vascular dose (2.5 mg twice daily) plus aspirin (100 mg once daily) was superior to aspirin alone in reducing the risk of major adverse limb and cardiovascular (CV) events by 15 percent in patients with symptomatic peripheral artery disease (PAD) after lower-extremity revascularization, with similar rates of TIMI[1] major bleeding. VOYAGER PAD is the only study to show a significant benefit using dual pathway inhibition, an

[1] Thrombolysis In Myocardial Infarction

anticoagulant plus aspirin, in this patient population. Findings from this global, randomized, double-blind, Phase 3 study were presented as a late-breaking presentation during the virtual American College of Cardiology's 69th Annual Scientific Session, together with the World Congress of Cardiology (ACC.20/WCC), and simultaneously published in *The New England Journal of Medicine*.

PAD is a common circulatory condition that occurs when narrowed blood vessels reduce blood flow to the limbs, most often the legs. PAD affects more than 200 million people globally,[ii] including eight million in the U.S.[iii] PAD is the leading cause of amputation[iv] and results in high rates of fatal and non-fatal CV events. Often starting as asymptomatic, PAD typically progresses to a more symptomatic, chronic form, with revascularization needed when symptoms become severe. Current PAD guidelines recommend antiplatelet therapy alone, such as aspirin or clopidogrel, to help prevent CV events[v,vi] following revascularization; however, no medicines are specifically indicated to prevent amputation or acute limb ischemia in these patients.

"While the COMPASS trial established the efficacy of rivaroxaban plus aspirin in stable patients with PAD and coronary artery disease (CAD), there were important unanswered questions on the optimal strategy for patients with symptomatic PAD after lower-extremity revascularization, including those without CAD. This is a particularly high-risk period for severe limb outcomes as well as bleeding," said Marc P. Bonaca, M.D., Department of Medicine, Division of Cardiovascular Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado. "The VOYAGER PAD study shows us the potential clinical utility of rivaroxaban 2.5 mg twice daily plus aspirin in preventing the most critical thrombotic complications, adverse limb and cardiovascular outcomes, during the post-revascularization period when PAD patients are most vulnerable to these serious events."

CLICK TO TWEET: Now available: New Phase 3 results show significant benefit of @JanssenUS medicine plus aspirin in patients with symptomatic #PAD after lower-extremity revascularization. Full press release here: http://bit.ly/3ddwFNr

The VOYAGER PAD results complement findings from the landmark Phase 3 COMPASS study, which also examined the dual pathway approach of XARELTO® (2.5 mg twice daily) plus aspirin (100 mg once daily). COMPASS found XARELTO® plus aspirin significantly reduced the risk of major CV and limb events in patients with chronic PAD and/or coronary artery disease (CAD) compared to aspirin alone.

"Our EXPLORER clinical research program continues to produce evidence of the critical role XARELTO® plays in helping to shape clinical practice and transform cardiovascular care," said James List, M.D., Ph.D., Global Therapeutic Area Head, Cardiovascular & Metabolism, Janssen Research & Development, LLC. "Based on the findings from the COMPASS and VOYAGER PAD studies, we believe a dual pathway approach of XARELTO® 2.5 mg twice daily dose plus aspirin can potentially change how PAD is managed. We look forward to discussing these data with the U.S. Food & Drug Administration (FDA)."

"Janssen continues to live up to our long-standing commitment of working tirelessly to bring transformational therapies to patients in need," said Mathai Mammen, M.D., Ph.D., Global Head of Janssen Research & Development, LLC, Johnson & Johnson. "XARELTO® has the potential to be the first anticoagulant in 20 years to show a benefit in patients with PAD after lower-extremity revascularization and is a strong example of that commitment."

VOYAGER PAD Results

For the primary efficacy endpoint, XARELTO® plus aspirin significantly reduced the risk of major adverse limb and CV events compared to aspirin alone. Specifically, researchers observed that nearly one in five patients taking aspirin alone suffered a major adverse limb or CV event, but this risk was significantly reduced by 15 percent when XARELTO® was added. The Kaplan-Meier (KM) estimates of the incidence at three years for XARELTO®/aspirin compared to aspirin alone were 17.3% vs. 19.9%, respectively (Hazard Ratio [HR]=0.85; 95% confidence interval [CI], 0.76-0.96; p=0.009). The benefit of adding XARELTO® to aspirin was

apparent early, was consistent among major subgroups and continued to accrue over time.

The principal safety endpoint was met, with no significant increase in TIMI major bleeding in patients treated with XARELTO® plus aspirin compared to aspirin alone. The KM estimates of the incidence at three years for XARELTO®/aspirin compared to aspirin alone were 2.65% vs. 1.87%, respectively (HR=1.43; 95% CI, 0.97–2.10; p=0.07). Of note, there were numerically fewer intracranial bleeding events in the XARELTO®/aspirin group (0.60% vs. 0.90%; HR=0.78; 95% CI, 0.38–1.61) and no increase in fatal bleeding (0.21% vs. 0.21%; HR=1.02; 95% CI, 0.33–3.15) across both groups.

About VOYAGER PAD

The Phase 3 VOYAGER PAD study included 6,564 patients from 542 sites across 34 countries worldwide. Patients were randomized in a 1:1 ratio and received either XARELTO® (2.5 mg twice daily) plus aspirin (100 mg once daily) (n=3,286) or aspirin alone (100 mg once daily) (n=3,278). Patients were stratified by revascularization procedure type (endovascular vs. surgical) and use of clopidogrel, which was administered at the treating physician's discretion. Patients were followed for a median of 28 months.

The primary efficacy endpoint was a composite of major adverse limb and CV events, including acute limb ischemia, major amputation for vascular causes, heart attack (myocardial infarction), ischemic stroke, or death from CV causes. The principal safety endpoint was major bleeding according to the TIMI classification.

Eligible patients were at least 50 years old and had documented symptomatic lower extremity PAD. Patients were eligible after a successful revascularization for symptomatic PAD within the last 10 days. Approximately two-thirds were treated with an endovascular procedure (65%) and one-third treated surgically (35%). Patients were excluded if they were clinically unstable, at heightened bleeding risk, or needed prohibited concomitant medications, including long-term clopidogrel. The

median age was 67 years and 26% were women. Common risk factors included diabetes, an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 (indicating mild-to-moderate kidney disease) and current smokers.

More on COMPASS

COMPASS, the largest clinical study of XARELTO® to date, enrolled a total of 27,395 patients with chronic CAD and/or PAD. Patients were randomized in a 1:1:1 ratio, with one group receiving XARELTO® (2.5 mg twice daily) plus aspirin (100 mg once daily), another group receiving XARELTO® 5 mg twice daily, and the final group receiving aspirin 100 mg once daily. COMPASS was stopped approximately one year ahead of schedule due to efficacy.

COMPASS met its primary efficacy endpoint, with XARELTO®/aspirin shown to be superior to aspirin alone, reducing major CV events by 24%. This finding was driven by a robust 42% reduction in any stroke and 22% reduction in CV death. While the risk of major bleeding was significantly higher in patients taking XARELTO®/aspirin compared to aspirin alone, there was no significant difference in fatal bleeds, intracranial bleeds, symptomatic bleeding into a critical organ, or bleeding into the surgical site requiring reoperation between the treatment groups.

WHAT IS XARELTO® (rivaroxaban)?

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) or peripheral artery disease (a condition where the blood flow to the legs is reduced)

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

IMPORTANT SAFETY INFORMATION

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 (an irregular heart beat) that is not caused by a heart valve problem (nonvalvular) 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 be at 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:
  - Nosebleeds that happen often
  - Unusual bleeding from 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), or 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.

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 of XARELTO®.

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

- Have 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® may 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®?"**

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**, XARELTO® **may be taken 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 or peripheral 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.

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 the FDA at 1-800-FDA-1088.** You may also report side effects to Janssen Pharmaceuticals, Inc., at 1-800-JANSSEN (1-800-526-7736).

Please read full Prescribing Information, including Boxed Warnings, and Medication Guide for XARELTO®.

About Janssen Cardiovascular & Metabolism

In Cardiovascular & Metabolism (CVM), we take on the most pervasive diseases that burden hundreds of millions of people and healthcare systems around the world. As part of this long-standing commitment and propelled by our successes in treating type 2 diabetes (T2D) and thrombosis, we advance highly differentiated therapies that prevent and treat life-threatening cardiovascular and metabolic diseases. Uncovering new therapies that can improve the quality of life for this large segment of the population is an important endeavor – one which Janssen CVM will continue to lead in the years to come. Our mission is global, local and personal. Together, we can reshape the future of cardiovascular and metabolic prevention and treatment. Please visit www.janssen.com/cardiovascular-and-metabolism.

About the Janssen Pharmaceutical Companies of Johnson & Johnson

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular & Metabolism, Immunology, Infectious Diseases & Vaccines, Neuroscience, Oncology, and Pulmonary Hypertension.

Learn more at www.janssen.com. Follow us at www.twitter.com/JanssenUS. Janssen Research & Development, LLC, is one of the Janssen Pharmaceutical Companies of Johnson & Johnson.

Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding rivaroxaban. The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Research & Development, LLC, any of the other Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended December 29, 2019, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's most recently filed Quarterly Report on Form 10-Q, and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any

forward-looking statement as a result of new information or future events or developments.

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