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New Phase 3 Data Suggest Positive Effect and Show Similar Safety with XARELTO® (rivaroxaban) Compared to Aspirin in Pediatric Fontan Procedure Patients at Risk for Blood Clots and Blood Clot-Related Events

Pivotal UNIVERSE study published in the Journal of the American Heart Association

Data included in recent New Drug Application submitted to FDA for two pediatric indications

RARITAN, NJ, September 27, 2021 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today new data from the Phase 3 UNIVERSE study showing treatment with XARELTO® (rivaroxaban) in an oral suspension formulation, compared to treatment with aspirin, was associated with numerically fewer blood clots and clinical events strongly associated with blood clots in pediatric patients (aged 2-8 years) who have undergone the Fontan procedure.[1] These findings, which were published this month in the *Journal of the American Heart Association* and included in a recent New Drug Application submitted to the U.S. Food and Drug Administration, also found treatment with XARELTO® was associated with a similar safety profile compared to aspirin.

[1] The UNIVERSE study was not powered to demonstrate efficacy results.

The Fontan procedure is performed in children with congenital heart disease who have a single functioning ventricle to redirect blood flow to the lungs to be reoxygenated. Children who undergo the Fontan procedure often face significant morbidity and mortality stemming from thrombotic events, especially during the critical 3- to 12-month period following the procedure. While it is common for physicians to prescribe aspirin, there are limited data regarding aspirin resistance or the optimal dose for thromboprophylaxis in children.

"For years, health care providers have had limited options to help reduce potentially fatal thrombotic events that often occur in young children following the Fontan procedure," said Brian W. McCrindle, M.D., MPH, Pediatric Cardiologist at the Hospital for Sick Children in Toronto.[i] "We now not only have data suggesting that rivaroxaban has a similar positive effect and safety as aspirin, but we also have identified an age-appropriate formulation with precise weight-based dosing to help manage our young patients during a critical time."

The UNIVERSE study was conducted to determine the comparative efficacy and safety of XARELTO® versus aspirin and to provide clear evidence-based dosing recommendations in this pediatric population.

The study was conducted in two parts: Part A evaluated pharmacokinetic (PK) and pharmacodynamic (PD) properties of XARELTO®, and Part B examined the safety and efficacy of XARELTO® compared to aspirin when used for thromboprophylaxis for 12 months. The primary safety outcome was major bleeding events defined by the International Society on Thrombosis and Haemostasis (ISTH). The secondary safety outcomes were clinically relevant non-major bleeding and trivial (minimal) bleeding events. The primary efficacy outcome was any thrombotic event (venous or arterial) defined as the appearance of a new thrombotic burden within the cardiovascular system noted on either routine surveillance or clinically indicated imaging, or the occurrence of a clinical event known to be strongly associated with

thrombus (e.g., stroke or pulmonary embolism). All thrombotic and safety events were adjudicated by the central independent adjudication committee (CIAC).

Key findings:

- A comparable and low prevalence of bleeding events was observed with XARELTO® compared to aspirin. There was one major non-fatal bleeding event (nosebleed) with XARELTO®, and compared to aspirin, a slightly lower prevalence of non-major clinically relevant bleeding (6 vs. 9 percent of participants) and trivial bleeding (33 vs. 35 percent of participants). The prevalence and pattern of adverse events were comparable between the two groups.
- There were fewer thrombotic events with XARELTO®, though the study was not powered for efficacy outcomes (post-hoc log-rank test p=0.095). In the XARELTO® group, one patient had a pulmonary embolism (2 percent event rate). In the XARELTO® Part A group, there was one venous thrombotic event for an overall rate of 3 percent in the XARELTO® groups combined. In the aspirin group, one participant had ischemic stroke and two had venous thrombosis (9 percent overall event rate).

"The promise of the EXPLORER research program for XARELTO® was to uncover new insights into how the medical community can help improve the care of patients who are faced with thrombotic risk, from young to old," said James List, M.D., Ph.D., Global Therapeutic Area Head, Cardiovascular, Metabolism, & Retina, Janssen Research & Development, LLC. "The UNIVERSE study is another example of our fulfillment of that promise, and we're optimistic these findings will generate greater understanding and help to inform guidance for physicians managing thrombotic complications in these vulnerable and high-risk pediatric patients."

UNIVERSE study design

A randomized, multicenter, open-label, active controlled, two-part, Phase 3 study, UNIVERSE examined the use of a novel, oral liquid suspension XARELTO® formulation in children 2-8 years old with single ventricle physiology who had the

Fontan procedure within four months before enrollment. From November 2016 to June 2019, 112 participants were enrolled across 35 sites in 10 countries.

During Part A of the study, PK and PD blood samples were collected on days 1 and 4 to determine if the patient could continue receiving the study drug for the 12-month study period. During Part B, patients were randomized in a 2:1 ratio to receive either body weight-adjusted XARELTO®, administered orally twice daily (dose regimen that matched the exposure range in adults treated with rivaroxaban 10 mg once daily), or aspirin, given once daily (approximately 5 mg/kg). The primary safety outcome was major bleeding events, and the primary efficacy outcome was any thrombotic event, including venous or arterial clots, or any thromboembolic event, including stroke or a pulmonary embolism. Patients had additional PK and PD samples collected at months 3 and 12. PK/PD results will be published at a later date.

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.

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:**
        - 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 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 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 and https://twitter.com/JanssenGlobal. 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 January 3, 2021, 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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[i] Dr. McCrindle is affiliated with the Hospital for Sick Children in Toronto, which was provided payment for their participation in the Phase 3 UNIVERSE clinical trial.

