



Media contacts:

Sarah Freeman
Mobile: (215) 510-4758
sfreem21@its.jnj.com

Andrew Wheatley
Mobile: (609) 664-1797
awheatle@its.jnj.com

Investor contacts:

Johnson & Johnson
Christopher DeLorefice
Office: (732) 524-2955

Lesley Fishman
Office: (732) 524-3922

XARELTO® (rivaroxaban) Helps Protect Pediatric Patients from Blood Clots in Late-Breaking Phase 3 EINSTEIN-Jr Study

EINSTEIN-Jr is the largest pediatric trial conducted for the treatment of venous thromboembolism (VTE) and the first to evaluate a direct oral anticoagulant in this population

RARITAN, N.J., July 8, 2019 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today new results from the Phase 3 EINSTEIN-Jr study, showing pediatric patients (aged birth to 17 years) treated with XARELTO® (rivaroxaban) had a similar low risk of recurrent venous thromboembolism (VTE) – or blood clots – and similar rates of bleeding when compared to current standard anticoagulation therapy. These results from the largest pediatric study ever conducted for the treatment of VTE also show that the efficacy and safety profile of XARELTO® in a pediatric population with VTE is comparable to what has been observed in previous studies of adults with VTE. The full findings were presented

during a late-breaking session at the 27th Congress of the International Society on Thrombosis and Haemostasis (ISTH) in Melbourne, Australia.

While VTE more commonly occurs in adults, it affects approximately 58 per 10,000 hospitalized children in the United Statesⁱ. There are very limited treatment options for these young patients, and no direct oral anticoagulant is currently approved for use in this setting. Current treatment is mainly based on observational data in this group and extrapolation of data obtained in adults, even though the pathophysiology and anatomic distribution (where it occurs in the body) of VTE, along with anticoagulant responses, differ between children and adults. Until EINSTEIN-Jr, only one small randomized trial had been published evaluating the use of standard anticoagulants in pediatric patients with VTE.ⁱⁱ Current guidelines recommend that young patients with VTE be treated with standard anticoagulation therapy. For these patients, physicians manipulate adult dosage forms of these older anticoagulants, many of which require injections and regular laboratory monitoring.

“This trial examined for the first time whether a direct oral anticoagulant could alleviate the burden of blood clots in young patients, which would allow them to focus on recovering from their other health challenges,” said Christoph Male, M.D., Department of Pediatrics, Medical University of Vienna, Vienna, Austria.¹ “The EINSTEIN-Jr study with rivaroxaban represents a significant advance for pediatric VTE treatment.”

[Click to Tweet: Results from the largest pediatric study ever conducted for the treatment of #bloodclots represent a significant advance for pediatric #VTE treatment https://ctt.ec/97800+](https://ctt.ec/97800+)

The main efficacy outcome of EINSTEIN-Jr was symptomatic recurrent VTE (fatal or non-fatal), and the principal safety outcome was the composite of major and clinically relevant non-major bleeding. The study met all of its prespecified endpoints.

¹ Dr. Christoph Male was compensated for his work on the EINSTEIN-Jr study.

The following observations were made:

- Recurrent VTE was similar in both treatment groups, with a numerically lower number of events in patients treated with XARELTO[®]. Specifically, 1.2 percent of the XARELTO[®] group and 3.0 percent of the standard anticoagulation group experienced a recurrent event (HR: 0.40; 95% CI, 0.11 to 1.41); there were no fatal VTE events in either treatment arm.
- Clinically relevant bleeding was also similar, occurring in 3.0 percent of the XARELTO[®] group and 1.9 percent of the standard anticoagulation group (HR: 1.58; 95% CI, 0.51 to 6.27). There were no major bleeding events in the XARELTO[®] group, and two major bleeding events in the standard anticoagulant group.
- In addition, the composite of recurrent VTE and major bleeding (net clinical benefit²) occurred in 1.2 percent of the XARELTO[®] group and 4.2 percent of the standard anticoagulation group (HR: 0.30; 95% CI, 0.08 to 0.93).

The efficacy of XARELTO[®] was further demonstrated by reduction in clot burden on imaging tests that were conducted on patients both at baseline and at the end of the treatment period. Complete resolution of the initial VTE mass occurred in 38.5 percent of the XARELTO[®] group compared to 26.1 percent of the standard anticoagulation group (Overall Response: 1.72; 95% CI, 1.12 to 2.69).

“VTE affects people of all ages, which is why we are committed to advancing new research and uncovering ways for XARELTO[®] to help people in need,” said James List, M.D., Ph.D., Global Therapeutic Area Head, Cardiovascular & Metabolism, Janssen Research & Development, LLC. “The EINSTEIN-Jr. results offer important insights on the efficacy and safety of XARELTO[®] in managing blood clots in our youngest patients.”

² Net clinical benefit is a quantitative assessment comparing the overall change in the benefits and risks of a medicine over a comparator medicine.

Study Background

Sponsored by Janssen and Bayer, EINSTEIN-Jr is the largest pediatric study conducted for the treatment of VTE, and the first to examine the use of a direct oral anticoagulant in this population. A Phase 3 randomized, open-label study, EINSTEIN-Jr evaluated the efficacy and safety of XARELTO® compared to standard anticoagulation therapy in 500 children aged birth to 17 years with previously diagnosed acute VTE who had started heparin therapy. Children were enrolled from 107 sites in 28 countries.

Participants were enrolled from November 2014 to September 2018 and were assigned in a 2:1 ratio to receive either an open-label, bodyweight-adjusted dose of XARELTO® (n=335) or standard anticoagulation therapy (n=165). Various tablet strengths and weight-based oral liquid suspension doses of XARELTO® were tested. Standard anticoagulants were given at therapeutic doses, according to international guidelines, and included unfractionated heparin, low-molecular-weight heparin (LMWH) or fondaparinux; following completion of five to nine days of standard anticoagulation, participants continued with heparin treatment or were switched to a vitamin K antagonist (VKA) at the discretion of the treating physician.

Approximately 90 percent of enrolled patients had conditions in which VTE is a known risk factor. Major surgery/trauma, major infectious diseases, major organ diseases and active cancer were among the most common conditions. For the index event, VTE was symptomatic in approximately 80 percent of participants and asymptomatic in approximately 20 percent. Of those enrolled, 23.4 percent had cerebral vein or sinus VTE, 25.4 percent had catheter-related VTE and 51.2 percent had other non-catheter-related VTE as their index event.

Participants were ineligible if they had active bleeding or were at high risk of bleeding contraindicating anticoagulant therapy, had a low platelet count, hepatic disease associated with a coagulopathy (bleeding disorder), severe renal impairment, or a life expectancy of less than three months. The main treatment

period was three months (or one month in children younger than two years with catheter-related VTE).

Prior to EINSTEIN-Jr, Phase 1 and 2 studies were conducted to establish bodyweight-adjusted dose regimens of XARELTO® for children aged birth to 17 years that matched the exposure range in adults younger than 45 years treated with XARELTO® 20-mg once daily. In addition to a tablet form of XARELTO®, an oral suspension formulation of XARELTO® was developed, with similar pharmacokinetic properties as the tablet formulation, which enabled precise dosing and easier administration especially in young children.

More on the Pediatric Program with XARELTO®

The Phase 3 EINSTEIN-Jr study is one of five from the pediatric research program for XARELTO® examining the use of the medicine in the management of VTE in children. A second key study, UNIVERSE, is evaluating XARELTO® for the prevention of VTE in children aged two to eight after the Fontan procedure, the most common procedure performed for congenital heart disease after the age of two years. XARELTO® is not currently approved by the U.S. Food and Drug Administration (FDA) for use in pediatric patients.

In adults, XARELTO® already has five approved VTE indications, the most of any direct oral anticoagulant, including the treatment of deep vein thrombosis (DVT), treatment of pulmonary embolism (PE), reduction of the risk of recurrent DVT and PE, and primary prevention of DVT which may lead to PE in people who have just had hip or knee replacement surgery. In October 2017, the FDA approved a new dose regimen of 10-mg XARELTO® once-daily for reducing the continued risk for recurrent VTE after completion of at least six months of initial therapy. The FDA is currently reviewing a supplemental New Drug Application (sNDA) for XARELTO® for the prevention of VTE in medically ill patients.

About the EINSTEIN Clinical Trial Program

The pivotal EINSTEIN program is comprised of five Phase 3 studies: EINSTEIN-DVT, EINSTEIN-PE, EINSTEIN-EXT, EINSTEIN CHOICE and EINSTEIN-Jr. EINSTEIN-DVT and EINSTEIN-PE evaluated XARELTO® versus the dual-drug regimen of LMWH and VKA for the treatment of DVT and PE, respectively, and the prevention of recurrent DVT and PE. EINSTEIN-EXT (or “Extension”) compared XARELTO® with placebo for the long-term prevention of recurrent DVT and PE in patients who previously completed six or 12 months of anticoagulation treatment with either VKA or XARELTO®. Finally, EINSTEIN CHOICE evaluated the long-term benefit of XARELTO® for the prevention of recurrent VTE compared to aspirin in patients who completed between six and 12 months of anticoagulant treatment for their index DVT or PE event.

About EXPLORER

A collaborative effort between Bayer and Janssen, our industry-leading EXPLORER program seeks to generate important clinical evidence on the safety and efficacy of XARELTO® and its potential role in addressing a wide range of critical medical needs. EXPLORER is unmatched by any oral anticoagulant in the Factor Xa inhibitor class in its size, scope and ambition.

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

XARELTO® is also used with low dose aspirin to:

- reduce the risk of serious heart problems, heart attack and stroke in patients with coronary artery disease (a condition where the blood supply to the heart is reduced or blocked) or peripheral arterial 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 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 people with artificial heart valves.**

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
- 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. You and your doctor should decide if you will take XARELTO® or breastfeed.

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

Tell your doctor about all the medicines you take, including prescription and 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.
- 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 **15-mg and 20-mg doses**, XARELTO® **should be taken with food.**
 - For the **10-mg dose**, XARELTO® **may be taken with or without food.**
 - Take your XARELTO® doses 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.

- **Reducing the risk of serious heart problems, heart attack and stroke in coronary artery disease or peripheral arterial disease:**
 - Take XARELTO® 2 times a day with or without food.
 - If you miss a dose of XARELTO®, take your next dose at your regularly scheduled time.
- If you have difficulty swallowing the XARELTO® tablet whole, talk to your doctor about other ways to take XARELTO®.
- Your doctor will decide how long you should take XARELTO®.
- XARELTO® may need to be stopped, if possible for one or more days before any surgery or medical/dental procedure. If you need to stop taking XARELTO® for any reason, talk to your doctor to find out when you should stop taking it. **Do not stop taking XARELTO® without first talking to the doctor who prescribed it to you.** Your doctor will tell you when to start taking XARELTO® again after your surgery or procedure.
- Do not run out of XARELTO®. Refill your prescription for XARELTO® before you run out. When leaving the hospital following a hip or knee replacement, be sure that you have XARELTO® available to avoid missing any doses.
- If you take too much XARELTO®, go to the nearest hospital emergency room or call your doctor right away.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF XARELTO®?

- The most common side effect of XARELTO® was bleeding.
- **See “What is the most important information I should know about XARELTO®?”**

Call your doctor for medical advice about side effects. **You may report side effects to 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 click [here](#) for full Prescribing Information, including Boxed Warnings, and Medication Guide.

Trademarks are those of their respective owners. Janssen and Bayer together are developing rivaroxaban. For more information about XARELTO®, visit www.xarelto.com.

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/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 XARELTO® (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 30, 2018, 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. Neither 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 Raffini L et al. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics*. 2009;124:1001-1008.

ⁱⁱ Massicotte P et al. An open-label randomized controlled trial of low molecular weight heparin compared to heparin and coumadin for the treatment of venous thromboembolic events in children: the REVIVE trial. *Thromb Res*. 2003;109:85-92.