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New Phase 3 Study Finds XARELTO® to Be Superior to Aspirin for Long-Term Prevention of Recurrent Blood Clots Without Observing any Significant Increase in Major Bleeding in Patients with Venous Thromboembolism

- *EINSTEIN CHOICE was presented as a late-breaker at the American College of Cardiology's 66th Annual Scientific Session and published simultaneously in* The New England Journal of Medicine
- *Phase 2 GEMINI-ACS-1 study also presented as a late-breaker and published simultaneously in* The Lancet*, showing similar safety between XARELTO® (rivaroxaban) and aspirin in patients with acute coronary syndrome also taking a P2Y12 inhibitor*

WASHINGTON, DC (March 18, 2017) – Janssen Pharmaceuticals, Inc. (Janssen) today announced new Phase 3 results from EINSTEIN CHOICE showing patients with venous thromboembolism (VTE) taking XARELTO® (rivaroxaban), who received either 10 mg or 20 mg once daily over an extended time period, had significantly fewer recurrent blood clots and similar rates of major bleeding compared to those taking aspirin 100 mg once daily. Specifically, XARELTO® 10 mg reduced the risk of recurrent VTE by 74 percent and XARELTO® 20 mg by 66 percent.

These findings were presented today during a Joint American College of Cardiology/*Journal of the American Medical Association* Late-Breaking Clinical Trials session at the American College of Cardiology's 66th Annual Scientific Session (ACC.17) and published simultaneously in The New England Journal of Medicine. EINSTEIN CHOICE is part of the industry-leading EXPLORER clinical research program for XARELTO®, a collaborative effort between Janssen and its development partner, Bayer.

VTE, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), affects more than 900,000 Americans each year; one-third of these occurrences are fatal.[i] As all people with VTE are at risk of having another occurrence, guidelines currently recommend anticoagulant therapy with a non-vitamin K antagonist oral anticoagulant (NOAC), like XARELTO®, for three months or longer.[ii]

Once anticoagulant therapy is stopped, up to 10 percent of people will experience a recurrence during the first year and up to 20 percent within three years.[iii] In people who decide to stop anticoagulant therapy, guidelines currently suggest using aspirin for long-term prevention of recurrent VTE rather than no aspirin at all.[ii] The EINSTEIN CHOICE study was designed to compare the efficacy and safety of XARELTO® to aspirin for continued VTE management.

"How best to extend anticoagulant use beyond the initial treatment window has been a constant source of debate, with physicians carefully balancing patients' risk of another VTE with the risk of anticoagulant-related bleeding," said study investigator Philip S. Wells, MD, Professor, Chair and Chief, Department of Medicine, University of Ottawa, and Senior Scientist, The Ottawa Hospital, Ontario, Canada. "With EINSTEIN CHOICE, for the first time we have clinical evidence confirming rivaroxaban is superior to aspirin in reducing recurrent VTE, with no significant impact on safety. These important results have the potential to trigger a paradigm shift in how physicians manage their patients and protect them from VTE recurrence over the long term."

EINSTEIN CHOICE met its primary endpoint, finding both XARELTO® doses (10 mg and 20 mg) to be superior to aspirin in preventing recurrent VTE. Researchers observed the following:

- The rate of recurrent VTE was 1.2 percent in the XARELTO® 10 mg group (HR=0.26; 95% CI, 0.14 to 0.47; p<0.001) and 1.5 percent in the XARELTO® 20 mg group (HR=0.34; 95% CI, 0.20 to 0.59; p<0.001) compared to 4.4 percent in the aspirin group. Fatal VTE occurred in 0 percent, 0.2 percent and 0.2 percent, respectively.
- Rates of major bleeding were comparable and low across all treatment groups at 0.4 percent for XARELTO® 10 mg (HR=1.64; 95% CI, 0.39 to 6.84; p=0.50), 0.5 percent for XARELTO® 20 mg (HR=2.01; 95% CI, 0.50 to 8.04; p=0.32) and 0.3 percent for aspirin. Rates of clinically relevant non-major bleeding also were similar between the groups at 2.0 percent, 2.7 percent and 1.8 percent, respectively.

Other efficacy outcomes were evaluated in the study. Researchers found 1.9 percent of the XARELTO® 10 mg group (HR=0.33; 95% CI, 0.20 to 0.54; p<0.001) and 2.0 percent of the XARELTO® 20 mg group (HR=0.35; 95% CI, 0.22 to 0.57; p<0.001) experienced either a recurrent VTE (primary efficacy endpoint), heart attack, ischemic stroke, systemic embolism or venous thrombosis in another location

compared to 5.6 percent of the aspirin group. Recurrent VTE or all-cause mortality occurred in 1.3 percent of the XARELTO® 10 mg group (HR=0.27; 95% CI, 0.15 to 0.47; p<0.001) and 2.1 percent of the XARELTO® 20 mg group (HR=0.42; 95% CI, 0.26 to 0.68; p<0.001) compared to 4.9 percent of the aspirin group. When looking at pre-specified subgroups, researchers found results for the primary efficacy endpoint (recurrent VTE) and composite outcome of major and clinically relevant non-major bleeding to be consistent with the overall findings.

"In addition to confirming findings from previous studies examining the long-term use of XARELTO® in VTE, EINSTEIN CHOICE provides valuable clinical insights on the superiority of XARELTO® to aspirin as well as the potential extended use of a lower dose of XARELTO® for continued venous protection," said Paul Burton, MD, PhD, FACC, Vice President, Medical Affairs, Janssen. "We look forward to discussing these important data with the U.S. Food and Drug Administration."

EINSTEIN CHOICE was led by principal investigator Jeffrey Weitz, MD, Professor of Medicine, Michael G. DeGroote School of Medicine, McMaster University, and Director of McMaster's Thrombosis & Atherosclerosis Research Institute. This Phase 3, global, randomized, double-blind, superiority study compared the efficacy and safety of two doses of XARELTO® (a prophylactic dose of 10 mg once daily and a treatment dose of 20 mg once daily) with aspirin 100 mg once daily for the continued management of VTE in people with confirmed DVT or PE who were initially treated with anticoagulant therapy for six to 12 months. Approximately 3,365 patients from 31 countries were included in the study analysis. Importantly, people who required extended anticoagulation at therapeutic doses were not included, as the objective of the study was to investigate those patients for whom the treating physician was uncertain about the need for continuing anticoagulant therapy.

Patients were randomized in a 1:1:1 ratio, with one group receiving XARELTO® 10 mg, another group receiving XARELTO® 20 mg, and a third receiving aspirin 100 mg, all given once daily for up to 12 months. Sixty percent of patients completed the full 12 months of treatment. The primary efficacy endpoint was fatal or non-fatal recurrent VTE (a composite of recurrent VTE, VTE-related death and unexplained death for which PE could not be excluded). The primary safety endpoint was major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH). Only the primary efficacy outcome comparisons of XARELTO® 10 mg vs. aspirin and XARELTO® 20 mg vs. aspirin were powered for significance. Comparison of the two XARELTO® arms was not powered for significance.

Late-Breaking Phase 2 GEMINI-ACS-1 Results

Also presented today during the same Joint American College of Cardiology/*Journal of the American Medical Association* Late-Breaking Clinical Trials session at ACC.17 and published simultaneously in The Lancet were results from the Phase 2 GEMINI-ACS-1 study, which investigated the safety of XARELTO® 2.5 mg twice daily compared to aspirin 100 mg once daily when added to a P2Y12 inhibitor (clopidogrel or ticagrelor) for the secondary prevention of cardiovascular events in patients with acute coronary syndrome (ACS). This early stage, double-blind, randomized study of 3,037 patients met its primary endpoint, showing similar safety with XARELTO® compared to aspirin in this ACS population. Specifically, GEMINI-ACS-1 researchers observed Thrombolysis in Myocardial Infarction (TIMI) clinically significant bleeding in 5.3 percent of the XARELTO® group and 4.9 percent of the aspirin group (HR=1.09; 95% CI, 0.80 to 1.50; p=0.58), with similar rates of severe/major bleeding (according to TIMI bleeding definitions) also noted between the groups.

Researchers also examined several exploratory efficacy endpoints. For the composite efficacy endpoint (which included cardiovascular death, heart attack, stroke or stent thrombosis), the two groups had similar rates, with 5.0 percent of the XARELTO® group and 4.7 percent of the aspirin group (HR=1.06; 95% CI, 0.77-1.46; p=0.73) experiencing a cardiovascular event. For all-cause death and the individual components of the composite efficacy endpoint, rates also were similar between the two groups.

"With slightly more than one million Americans discharged from the hospital each year with either a primary or secondary diagnosis of ACS,[iv] it is important for the scientific community to continue investigating different treatment approaches for vascular protection aimed at preventing secondary cardiovascular events in these patients," said Dr. Burton. "Results from this preliminary study find XARELTO® and aspirin to have similar safety post-ACS, and we intend to use this research to inform future plans for examining XARELTO® in this population."

About EXPLORER

Both EINSTEIN CHOICE and GEMINI-ACS-1 are part of the EXPLORER clinical research program for XARELTO®. The EXPLORER program is unmatched by any oral anticoagulant in the NOAC class in its size, scope and ambition. A collaborative effort between Janssen and Bayer, EXPLORER seeks to generate important clinical evidence on the safety and efficacy of XARELTO® and its potential role in addressing critical unmet medical needs. A number of the studies are designed to seek additional indications or expand the label for XARELTO®. By the time of its completion, more than 275,000

patients will have participated in the EXPLORER clinical development program, other completed and ongoing clinical trials, investigative registries and non-interventional studies.

WHAT IS XARELTO®?

XARELTO® is a prescription medicine used to reduce the risk of stroke and blood clots in people with atrial fibrillation, not caused by a heart valve problem. For patients currently well managed on warfarin, there is limited information on how XARELTO® and warfarin compare in reducing the risk of stroke.

XARELTO® is also a prescription medicine used to treat deep vein thrombosis and pulmonary embolism, and to help reduce the risk of these conditions occurring again.

XARELTO® is also a prescription medicine used to reduce the risk of forming a blood clot in the legs and lungs of people who have just had knee or hip replacement surgery.

IMPORTANT SAFETY INFORMATION

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT XARELTO®?

- **For people taking XARELTO® for atrial fibrillation**:

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

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

  If you have to stop taking XARELTO®, your doctor may prescribe another blood thinner medicine to prevent a blood clot from forming.

- **XARELTO® can cause bleeding**, which can be serious, and rarely may lead to death. This is because XARELTO® is a blood thinner medicine that reduces blood clotting. While you take XARELTO® you are likely to bruise more easily and it may take longer for bleeding to stop.

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

- Aspirin or aspirin-containing products
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Warfarin sodium (Coumadin®, Jantoven®)
- Any medicine that contains heparin
- Clopidogrel (Plavix®)
- Selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)
- Other medicines to prevent or treat blood clots

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

Call your doctor or get medical help right away if you develop any of these signs or symptoms of bleeding:

- Unexpected bleeding or bleeding that lasts a long time, such as:
    - Nosebleeds that happen often
    - Unusual bleeding from gums
    - Menstrual bleeding that is heavier than normal, or vaginal bleeding
- Bleeding that is severe or that 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 patients with artificial heart valves.

WHO SHOULD NOT TAKE XARELTO®?

Do not take XARELTO® if you:

- Currently have certain types of abnormal bleeding. Talk to your doctor before taking XARELTO® if you currently have unusual bleeding.
- Are allergic to rivaroxaban or any of the ingredients of XARELTO®.

WHAT SHOULD I TELL MY DOCTOR BEFORE OR WHILE TAKING XARELTO®?

Before taking XARELTO®, tell your doctor if you:

- Have ever had bleeding problems
- Have liver or kidney problems
- Have any other medical condition
- Are pregnant or plan to become pregnant. It is not known if XARELTO® will harm your unborn baby. Tell your doctor right away if you become pregnant while taking XARELTO®. If you take XARELTO® during pregnancy, tell your doctor right away if you have bleeding or symptoms of blood loss.
- Are breastfeeding or plan to breastfeed. It is not known if XARELTO® passes into your breast milk. You and your doctor should decide if you will take XARELTO® or breastfeed.

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

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Some of your other medicines may affect the way XARELTO® works. Certain medicines may increase your risk of bleeding. **See "What is the most important information I should know about XARELTO®?"**

Especially tell your doctor if you take:

- Ketoconazole (Nizoral®)
- Itraconazole (Onmel™, Sporanox®)
- Ritonavir (Norvir®)
- Lopinavir/ritonavir (Kaletra®)
- Indinavir (Crixivan®)
- Carbamazepine (Carbatrol®, Equetro®, Tegretol®, Tegretol®-XR, Teril™, Epitol®)
- Phenytoin (Dilantin-125®, Dilantin®)
- Phenobarbital (Solfoton™)
- Rifampin (Rifater®, Rifamate®, Rimactane®, Rifadin®)
- St. John's wort (*Hypericum perforatum*)

Ask your doctor if you are not sure if your medicine is one listed above. Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

HOW SHOULD I TAKE XARELTO®?

Take XARELTO® exactly as prescribed by your doctor.

Do not change your dose or stop taking XARELTO® unless your doctor tells you to.

- Your doctor will tell you how much XARELTO® to take and when to take it.
- Your doctor may change your dose if needed.

If you take XARELTO® for:

- **Atrial Fibrillation:** Take XARELTO® 1 time a day with your evening meal.
  If you miss a dose of XARELTO®, take it as soon as you remember on the same day.
  Take your next dose at your regularly scheduled time.
- **Blood clots in the veins of your legs or lungs:**
  - Take XARELTO® once or twice a day as prescribed by your doctor.
  - Take XARELTO® with food at the same time each day.
  - If you miss a dose of XARELTO®:
    - **and take XARELTO® 2 times a day:** Take XARELTO® as soon as you remember on the same day. You may take 2 doses at the same time to make up for the missed dose. Take your next dose at your regularly scheduled time.
    - **and take XARELTO® 1 time a day:** Take XARELTO® as soon as you remember on the same day. Take your next dose at your regularly scheduled time.
- **Hip or knee replacement surgery:** Take XARELTO® 1 time a day with or without food.
  If you miss a dose of XARELTO®, take it as soon as you remember on the same day.
  Take your next dose at your regularly scheduled time.

- If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take XARELTO®.
- Your doctor will decide how long you should take XARELTO®**.** Do not stop taking XARELTO® without talking to your doctor first.
- Your doctor may stop XARELTO® for a short time before any surgery, medical or dental procedure. Your doctor will tell you when to start taking XARELTO® again after your surgery or procedure.

- Do not run out of XARELTO®. Refill your prescription 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®?

Please see "What is the most important information I should know about XARELTO®?"

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

Call your doctor for medical advice about side effects. You are also encouraged to report side effects to the FDA: visit *http://www.fda.gov/medwatch* or call 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

At the Janssen Pharmaceutical Companies of Johnson & Johnson, we are working to create a world without disease. Transforming lives by finding new and better ways to prevent, intercept, treat and cure disease inspires us. We bring together the best minds and pursue the most promising science. We are Janssen. We collaborate with the world for the health of everyone in it. Learn more at www.janssen.com. Follow us at @JanssenUS.

**As an investigator, Dr. Wells was compensated for his role in the study, but not for time spent on media interviews.*

Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding product development, including the potential impact of clinical findings on the use of rivaroxaban in continued VTE management. 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 Pharmaceuticals, Inc. or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges inherent in product research and development, including uncertainty of clinical success and obtaining regulatory approvals; competition, including technological advances, new products and patents attained by competitors; challenges to patents; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and description 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 1, 2017, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors", 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 or 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] Heit JA, Cohen AT, Anderson FA, Jr. Estimated annual number of incident and recurrent, non-fatal and fatal venous thromboembolism (VTE) events in the US. *Blood* 2005 November 16;106(11):267A (Abstract #910).

[ii] Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease CHEST Guideline and Expert Panel Report. *CHEST* 2016;149(2):315-52.

[iii] Douketis J, Tosetto A, Marcucci M, Baglin T, Cosmi B, Cushman M, et al. Risk of recurrence after venous thromboembolism in men and women: patient level meta-analysis. *BMJ* 2011;342:d813.

[iv] Benjamin EJ et al on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association. *Circulation 2017; CIR.0000000000000485;* Originally published January 25, 2017.