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New Phase 3 CASSINI Data Presented on the Use of XARELTO® (rivaroxaban) for Venous Thromboembolism (VTE) Prevention in High-Risk Cancer Patients

VTE is the second leading cause of death in people with cancer

SAN DIEGO, December 4, 2018 — The Janssen Pharmaceutical Companies of Johnson & Johnson today announced important new data from the Phase 3 CASSINI study on the use of oral anticoagulant XARELTO® (rivaroxaban) in the management and prevention of VTE (or blood clots) in high-risk patients with cancer. The composite primary endpoint of VTE occurrence did not reach statistical significance during the full study period. However, use of XARELTO® resulted in a clinically meaningful and nominally significant 60 percent reduction of VTE events compared to placebo during the time patients were actively receiving treatment. Bleeding rates were low, though higher with XARELTO®. These late-breaking results, presented this week at the 60th American Society of Hematology (ASH) Annual

Meeting in San Diego, add to the robust research from prior XARELTO® trials.

Click to Tweet: New data presented on the use of Janssen's #bloodthinner for preventing #bloodclots in high-risk patients with #cancer #ASH18 #VTE https://ctt.ec/AquXe+

"We want patients to focus on treating their cancer and getting better, without the concern and burden of blood clots," said Alok Khorana, M.D., FACP, Sondra and Stephen Hardis Chair in Oncology, Vice Chair for Clinical Services, Director of the GI Malignancies Program, Cleveland Clinic, and CASSINI lead investigator. "Building on prior research supporting the use of rivaroxaban for the treatment of VTE in patients with cancer, this new CASSINI data signal the role of rivaroxaban in preventing blood clots." Dr. Khorana was compensated by Janssen for his role as chair of the CALLISTO advisory council and co-chair of the CASSINI steering committee.

Despite being largely preventable, blood clots remain the second leading cause of death in patients with cancer. The risk of VTE, which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE), is five times greater in people with cancer, and that risk is magnified in those receiving certain types of chemotherapy.[1] VTE risk is also highest in the newly diagnosed and in those with more advanced, metastatic disease.[2] Recent guidelines issued by the International Society on Thrombosis and Haemostasis (ISTH) and National Comprehensive Cancer Network (NCCN) recommend XARELTO® as an option for the treatment of cancer-associated VTE. Currently, no medicine is approved for the primary prevention of VTE in high-risk, ambulatory cancer patients, due to limited clinical data.

"We are very encouraged by the CASSINI results and look forward to discussing them with the Food & Drug Administration," said Paul Burton, M.D., Ph.D., FACC, Vice President, Medical Affairs, Internal Medicine, Janssen Scientific Affairs, LLC. "This study underscores our longstanding commitment to exploring the full potential of XARELTO® through our EXPLORER program. Most recently, XARELTO® became

the first and only Factor Xa inhibitor indicated for people with chronic coronary or peripheral artery disease."

Study Results

In the intent to treat (ITT) population, the primary efficacy composite endpoint (symptomatic or asymptomatic lower-extremity proximal DVT, symptomatic upper-extremity or distal lower-extremity DVT, symptomatic or incidental PE, and VTE-related death) occurred during the study period in 8.79 percent of patients in the placebo group and in 5.95 percent of patients treated with XARELTO® 10 mg once daily; however, this result was not statistically significant (HR=0.66; 95% CI, 0.40-1.09; p=0.101). Approximately 62.4 percent of patients completed the double-blind trial period from randomization through the end of the study's 180-day observation period, regardless of whether they discontinued the study medication. Withdrawal of consent and death were the primary reasons for discontinuation.

Researchers also examined the primary efficacy composite endpoint in all randomized patients, during the time they were actively taking treatment, known as the 'on-treatment' period. For this pre-specified analysis, XARELTO® was associated with a statistically significant 60 percent reduction in VTE events compared to placebo (2.62 percent vs. 6.41 percent; HR=0.40; 95% CI, 0.20-0.80; p=0.007). The primary safety outcome, ISTH major bleeding, during the on-treatment period was low across both treatment arms and occurred in 4/404 (0.99 percent) patients treated with placebo and 8/405 (1.98 percent) patients treated with XARELTO®; this result was not statistically significant, though the study was not powered to detect a significant difference. (HR=1.96; 95% CI, 0.59-6.49; p=0.265).

<u>The following observations were also made</u>:

- Of the total VTE events that occurred, approximately 39 percent were experienced by patients who had prematurely discontinued treatment.
- All-cause mortality, a secondary efficacy endpoint, was similar between both groups at the end of the 180-day observation period (20.0 percent for

XARELTO® vs. 23.8 percent for placebo; HR=0.83; 95% CI, 0.62-1.11). Many patients died as a result of their cancer, with a small number of VTE-related deaths.

- Efficacy and safety outcomes were consistent across all prespecified subgroups.

Prior XARELTO® Research in Cancer-Associated VTE

The CASSINI results add to prior research on the use of XARELTO® in people with cancer. A prospective, randomized, open-label, multicenter pilot trial of 406 patients with cancer diagnosed with acute VTE, SELECT-D, found XARELTO® was associated with significantly lower rates of recurrent VTE compared to low-molecular weight heparin (LMWH) (4 percent vs. 11 percent; HR=0.43; 95% CI, 0.19-0.99). However, six-month cumulative major bleeding rates were higher in the XARELTO® group (6 percent vs. 4 percent; HR=1.83; 95% CI, 0.68-4.96) as were rates of clinically relevant non-major bleeding (13 percent vs. 4 percent; HR=3.76; 95% CI, 1.63-8.69).

Additional Information About CASSINI

CASSINI is a Phase 3b, randomized, double-blind, placebo-controlled, parallel-group superiority study comparing the efficacy and safety of XARELTO® with placebo for the primary prevention of VTE in adult patients with active cancer who were scheduled to receive systemic cancer therapy, like chemotherapy, outside the hospital setting. A total of 841 patients were randomized in a 1:1 ratio, with 420 receiving XARELTO® 10 mg once daily and 421 receiving placebo. Of all patients randomized, 43.7 percent prematurely discontinued XARELTO® and 50.2 percent prematurely discontinued placebo during the study's 180-day observation period; reasons for discontinuation were similar between groups. Patients were at high risk of developing VTE, with a baseline Khorana risk score of ≥2 (a recognized scoring system for predicting VTE in cancer patients). Patients had various types of solid cancers or lymphoma and were stratified by tumor type (advanced pancreatic cancer (APC) or non-APC). Patients also had an expected survival of greater than six months with a plan to start a new systemic regimen within one week of

initiating study treatment. A total of 1,080 patients from 143 sites across 11 countries were enrolled and underwent a screening compression ultrasound prior to randomization; of these, 49 patients had evidence of DVT and were excluded from the study.

CASSINI consisted of three periods: a two-week screening period; a 180-day double-blind treatment period; and a 30-day post-treatment follow-up period with a day 210/end-of-study visit. During the double-blind treatment period, study visits occurred during week 8, week 16 and week 26/end of treatment, with compression ultrasounds conducted at each visit to assess VTE occurrence. The study used an ITT population, which means that all participants were followed during the 180-day observation period, regardless of whether they took or prematurely discontinued study medicine.

About CALLISTO and EXPLORER

CASSINI is part of the CALLISTO research program, the largest and broadest prospective clinical program evaluating a Factor Xa inhibitor, specifically XARELTO®, for the prevention and treatment of cancer-associated VTE. It includes clinical trials and registries in more than 4,000 patients. CALLISTO also further examines findings from the Phase 3 EINSTEIN clinical program, which was used by regulatory authorities worldwide to approve XARELTO® for the treatment of VTE and reduction of risk of recurrent VTE.

CALLISTO is part of the EXPLORER clinical research program for XARELTO®. A collaborative effort between Janssen and its development partner Bayer, EXPLORER seeks to generate important clinical evidence on the safety and efficacy of XARELTO® and its potential role in addressing critical medical needs. Several studies in the program are designed to seek additional indications or expand the label for XARELTO® to benefit more patients in need of additional therapies for their cardiovascular disease. 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 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 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

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 on Twitter at @JanssenUS. Janssen Pharmaceuticals, Inc. and Janssen Scientific Affairs, LLC are part 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 product development and the presentation of new data and analyses 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 Pharmaceuticals, Inc., Janssen Scientific Affairs, 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 31, 2017, 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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[1] National Blood Clot Alliance: Stop the Clot (August 6, 2018). Cancer and Blood Clots – Fast Facts. https://www.stoptheclot.org/about-clots/cancer-and-blood-clots/cancer-and-blood-clots-fast-facts/.
[2] Qureshi W et al. Venous Thromboembolism in Cancer: An Update of Treatment and Prevention in the Era of Newer Anticoagulants. *Front Cardiovasc Med.* 2016;3:24.