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Janssen Announces Results from MARINER and COMMANDER HF Studies

Company sees a filing pathway for approval in acute medically ill

MUNICH, August 27, 2018 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced the results of the Phase 3 MARINER and COMMANDER HF (heart failure) studies, which were presented this week at the European Society of Cardiology (ESC) Congress 2018 and simultaneously published in *The New England Journal of Medicine.* In both studies, there was no significant difference found between XARELTO® (rivaroxaban) and placebo for the primary efficacy endpoints. XARELTO® did, however, demonstrate a consistent safety profile.

MARINER demonstrated that XARELTO® did not reduce the composite endpoint of venous thromboembolism (VTE), or blood clots, and VTE-related death in acute medically ill patients following hospital discharge. However, XARELTO® did significantly reduce VTE with consistent safety, reinforcing the medicine's positive

benefit-risk profile. An earlier clinical trial (MAGELLAN) evaluated the use of XARELTO® in the same population of acute medically ill patients as in MARINER.

"Beyond the three already approved VTE indications for XARELTO®, the combination of results from MARINER and MAGELLAN tell a more complete story about its role in preventing VTE in appropriate acute medically ill patients, both in-hospital and post-discharge," said James List, M.D., Ph.D., Global Therapeutic Area Head, Cardiovascular & Metabolism, Janssen Research & Development, LLC. "We see a filing pathway towards approval with these combined findings and look forward to discussing them with the U.S. Food and Drug Administration (FDA)."

In COMMANDER HF, XARELTO® did not impact overall mortality outcomes compared to standard of care. However, there were numerically fewer heart attacks and strokes with XARELTO® in sick patients with significant coronary artery disease (CAD) and reduced left ventricular ejection fraction (LVEF) who experienced a recent episode of acute decompensated heart failure (ADHF). These results suggest that the high death rate in these patients is primarily driven by poor heart function, and not thrombotic events.

The MARINER and COMMANDER HF studies are part of XARELTO®'s differentiated and industry-leading clinical development program EXPLORER, which evaluates the potential role of XARELTO® in treating a wide range of critical medical needs.

"We initiated the EXPLORER program to understand the full potential of XARELTO®. We've already filed an application to the FDA for two new indications based on the COMPASS trial, which stopped a year early for efficacy, and we look forward to sharing data from the upcoming CASSINI and VOYAGER PAD studies," said Dr. List. "XARELTO® has been approved for a variety of indications and prescribed more than 42 million times worldwide since its launch. Building off this strong foundation, these findings from the COMMANDER HF and MARINER trials will help the scientific community better understand the underlying role of thrombosis in morbidity and mortality across many different disease states."

Johnson & Johnson will conduct a conference call with investors to discuss this news release today, August 27, 2018 at 8 a.m. Eastern Time.

MARINER Results

In the study, researchers found no significant difference between XARELTO® and placebo for the primary efficacy endpoint, which was a composite of VTE and VTE-related death (0.83% for XARELTO® vs. 1.1% for placebo; HR=0.76; 95% CI, 0.52-1.09; p=0.136). However, when examining VTE only, fewer VTE events were observed with XARELTO® (0.18% vs. 0.42%; HR=0.44; 95% CI, 0.22-0.89; p=0.023). Fewer events were also observed with XARELTO® in the exploratory secondary composite endpoint of symptomatic VTE and all-cause mortality (1.3% vs. 1.78%; HR=0.73; 95% CI, 0.54-0.97; p=0.033). Major bleeding occurred infrequently and was not significantly different between XARELTO® and placebo (0.28% vs. 0.15%; HR=1.88; 95% CI, 0.84-4.23; p=0.124), though the study was not powered to detect differences in this measure; however, non-major clinically relevant bleeding was higher in the XARELTO® group (1.42% vs. 0.85%; HR=1.66; 95% CI, 1.17-2.35; p=0.004).

"Acute medically ill patients discharged from the hospital are at risk of VTE up to six weeks after hospital discharge, even though these events are largely preventable," said Alex C. Spyropoulos[i], M.D., Professor of Medicine, The Donald and Barbara Zucker School of Medicine, Northwell Health at Lenox Hill Hospital, New York, NY. "Exploratory analyses of symptomatic VTE in the MARINER study, which included non-fatal pulmonary embolism (PE), suggest a benefit with rivaroxaban. Given the very low rates of major bleeding with rivaroxaban, these overall findings give us important insight into the optimization of treatment strategies for preventing VTE in acute medically ill people once they leave the monitored care of a hospital."

COMMANDER HF Results

The COMMANDER HF study evaluated XARELTO® in reducing the risk of heart attack, stroke and death after an episode of ADHF in patients who have had symptomatic HF for at least three months. In the study, researchers found no significant difference in the primary efficacy endpoint, which was a composite of heart attack, stroke and all-cause death, between XARELTO® plus standard of care compared to standard of care alone (25% vs. 26.2%; HR=0.94; 95% CI, 0.84-1.05; p=0.270). However, patients taking XARELTO® were observed to have numerically fewer heart attacks (3.9% vs. 4.7%; HR=0.83; 95% CI, 0.63-1.08; p=0.165) and strokes (2.0% vs. 3.0%; HR=0.66; 95% CI, 0.47-0.95; p=0.023) compared to standard of care alone.

Importantly, the composite endpoint was driven primarily by all-cause death, which comprised 80 percent of the primary endpoint in both groups. In addition, fatal bleeding or bleeding into a critical space (like an organ) was similar between the two groups (0.7% vs. 0.9%; HR=0.80; 95% CI, 0.43-1.49; p=0.484), but non-major clinically relevant bleeding was higher in the XARELTO® group (3.3% vs. 2.0%; HR=1.68; 95% CI, 1.18-2.39; p=0.003).

"Given the high mortality rates after an episode of worsening heart failure, we explored whether reducing thrombotic events through anticoagulation would lead to better overall outcomes for patients compared to standard of care alone," said Faiez Zannad[ii], M.D., Ph.D., FESC, Professor of Therapeutics and Cardiology, Inserm Clinical investigation center, CHU and University de Lorraine, Nancy, France. "COMMANDER HF demonstrated that rivaroxaban did not impact overall mortality outcomes, suggesting the high death rate in these very sick patients is primarily driven by poor heart function and not thrombotic events."

About MARINER

Sponsored by Janssen, MARINER was a randomized, double-blind, placebo-controlled study in acute medically ill patients. "Acute medically ill" is a broad term that describes people who are hospitalized for serious yet common medical conditions, such as HF, infectious diseases or ischemic stroke. These patients are at

increased risk for VTE, both during their hospital stay and for up to three months after discharge. In fact, 67 percent of recently hospitalized patients who develop a VTE do so within one month of discharge.[ii] Evidence-based guidelines currently recommend that people at risk of VTE receive anticoagulants in the hospital, but advise against routine anticoagulant use beyond the hospital stay.

The study was conducted at 671 centers in 36 countries. A total of 12,019 patients were randomized in a 1:1 ratio, with one group receiving XARELTO® (n=6,007) and the other group receiving placebo (n=6,012), beginning at the time of hospital discharge and continuing for 45 days. For patients receiving XARELTO®, those with normal or mildly impaired renal function (CrCl ≥50 ml/min) received 10 mg once daily; those with moderate renal impairment (CrCl ≥30 ml/min and <50 ml/min) received 7.5 mg once daily. Patients with moderate renal impairment comprised 18 percent of the total population.

To be eligible, patients had to be 40 years of age or older and hospitalized between three and 10 days for serious medical conditions, including HF, chronic obstructive pulmonary disease (COPD), acute ischemic stroke, acute infectious diseases, or inflammatory diseases, including rheumatic disease. Patients also needed to be at increased risk of VTE, as determined by an IMPROVE VTE (International Medical Prevention Registry On Venous Thromboembolism) risk score of four or more, or by an IMPROVE VTE risk score of two or three plus a plasma D-dimer level of more than twice the upper limit of normal. Patients with medical conditions requiring anticoagulants, or a history of recent bleeding or high risk of bleeding due to concomitant conditions, drugs or procedures, were excluded from the study.

Mean age of study participants was 69.7 years. Randomization occurred on the same day or the day after hospital discharge. All participants were seen in person on days 21 and 45, and contact also was made on day seven with a final contact on day 75. The primary efficacy endpoint was the composite of all symptomatic VTE events, including lower extremity deep vein thrombosis (DVT), non-fatal PE, and

VTE-related death. The primary safety endpoint was major bleeding according to International Society on Thrombosis and Haemostasis (ISTH) bleeding criteria.

Since superiority was not established in the primary composite efficacy analysis, the prespecified secondary efficacy outcomes were assessed as exploratory analyses. Secondary efficacy endpoints included: VTE-related death; symptomatic VTE; composite of symptomatic VTE and all-cause death; composite of symptomatic VTE, heart attack, non-hemorrhagic stroke and cardiovascular (CV) death; and all-cause mortality. Other safety outcomes were non-major clinically relevant bleeding and other bleeding.

About MAGELLAN

Prior to MARINER, Janssen evaluated the use of XARELTO® 10 mg in preventing VTE in a similar population of acute medically ill patients, starting with their hospital stay and continuing through post-hospital discharge. This earlier Phase 3 trial met its two co-primary endpoints, with XARELTO® demonstrating non-inferiority to enoxaparin in short-term use (10 ± 4 days) and superiority in long-term use (35 ± 4 days) compared to short-term use of enoxaparin followed by placebo. The combined rates of major and non-major clinically relevant bleeding were higher in those treated with XARELTO®.

About COMMANDER HF

Sponsored by Janssen, COMMANDER HF was an international, prospective, multi-center, randomized, double-blind, placebo-controlled, event-driven study. Conducted at 628 sites in 32 countries, this study is the first randomized trial to explore the role of a Factor Xa inhibitor in patients with HF. Patients with significant valvular heart disease or atrial fibrillation before randomization were excluded.

Approximately 6.5 million Americans have HF, and this number is expected to increase. Hospitalization is very common after HF diagnosis, with research showing 83 percent of patients hospitalized at least once and 43 percent hospitalized at

least four times. Mortality rates after hospitalization for HF are 10.4 percent, 22 percent and 42.3 percent at 30 days, one year and five years, respectively.[iii]

The study enrolled 5,022 patients after they were hospitalized for ADHF. Patients were randomized in a 1:1 ratio, with one group (n=2,507) receiving XARELTO® 2.5 mg twice daily plus standard of care and the other group (n=2,515) receiving placebo plus standard of care. Standard of care was at the treating physician's discretion and could include aspirin or dual antiplatelet therapy.

To be eligible, participants over the age of 18 had to be treated for an episode of ADHF – also known as worsening heart failure – requiring intravenous diuretics or hospitalization within the previous 21 days. They also had to have symptomatic HF for at least three months, significant CAD and a LVEF of less than 40 percent. LVEF measures the amount of blood that is pumped out of the left ventricle with each heartbeat, with normal levels ranging from 55-70 percent. Patients receiving anticoagulation for other chronic conditions were also excluded.

The mean age of study participants was 66.4 years. The majority of patients had concomitant conditions, with approximately 75.7 percent having a history of heart attack, 75.3 percent having hypertension and 40.9 percent having a history of diabetes. All patients were seen at randomization (day 1), weeks four and 12, and every 12 weeks after that, with a final visit within 30 days before the end of the trial.

The primary efficacy endpoint was the composite of heart attack, stroke and all-cause death. The primary safety endpoint was the composite of fatal bleeding or bleeding into a critical space with potential for permanent disability. Secondary efficacy endpoints included the composite of CV death and rehospitalization for ADHF, as well as the separate outcomes of CV death, rehospitalization for ADHF, and rehospitalization for CV events. Additional safety endpoints included bleeding events requiring hospitalization and major bleeding events according to ISTH bleeding criteria.

About EXPLORER

MARINER and COMMANDER HF are both part of the EXPLORER clinical research program for XARELTO®. A collaborative effort between Janssen and its development partner Bayer, EXPLORER generates important clinical evidence on the safety and efficacy of XARELTO®. Many studies in the program are designed to seek additional indications or expand the label for XARELTO® to benefit more patients in need of therapies for their CV disease. By the time of its completion, more than 275,000 patients will have participated in the EXPLORER program, other completed and ongoing clinical trials, investigative registries and non-interventional studies.

Johnson & Johnson to Host Investor Conference Call

A conference call and simultaneous webcast for investors and other interested parties may be accessed by visiting the Johnson & Johnson website at www.investor.jnj.com. A replay and podcast will be available approximately three hours after the live webcast by visiting www.investor.jnj.com.

WHAT IS XARELTO®?

XARELTO® (rivaroxaban) 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 (DVT) and pulmonary embolism (PE), and to 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.

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® (rivaroxaban)?

- **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 (anticoagulant) 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 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 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. 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:**
        - 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® dose(s) 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.
- 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®.
- 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®?

- **See "What is the most important information I should know about XARELTO®?"**

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.

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 and @JanssenGlobal. Janssen Research & Development, LLC is 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 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 31, 2017, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," in the company's most recently filed Quarterly Report on Form 10-Q, and in the company's other 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] Dr. Alex C. Spyropoulos and Dr. Faiez Zannad worked directly with Janssen R&D and were compensated for their work on the MARINER and COMMANDER HF studies, respectively.

[ii] Spencer FA, Lessard D, et al. Venous thromboembolism in the outpatient setting. *Arch Intern Med.* 2007;167(14):1471-75.

[iii] Benjamin EJ, Virani SS, et al. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. *Circulation.* 2018;137:e67-e492.