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Clinical Trial Data Evaluating a Treatment for Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE) in Patients With Active Cancer

Announcer:
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This medical industry feature, titled "Clinical Trial Data Evaluating a Treatment for Deep Vein Thrombosis (or DVT) and/or Pulmonary Embolism (or PE) in Patients With Active Cancer," is a promotional educational activity brought to you by Janssen Pharmaceuticals, Inc., and is not certified for continuing medical education. The consultants are paid speakers for Janssen Pharmaceuticals, Inc. The speakers are presenting on behalf of Janssen and must present information in compliance with FDA requirements applicable to Janssen.

Here's your host, Dr Jennifer Caudle.

Dr Caudle:
Venous thromboembolism, or VTE, is a condition that most often manifests as deep vein thromboses and pulmonary embolisms, the latter of which can be fatal if not treated quickly and effectively. For patients already diagnosed with other debilitating diseases, such as cancer, the risk of severe complications from VTE becomes even greater. On today's program, we'll explore what the latest clinical trial data are telling us about one treatment option for these patients.

This is ReachMD, and I'm your host, Dr Jennifer Caudle, and joining me today to discuss clinical trial data evaluating the treatment of VTE in patients with active cancer, is Dr Steven Fein. Dr Fein is a hematologist/oncologist and a clotting specialist at Heme Onc Call in Miami, Florida.

Dr Fein, thank you so much for being here today.

Dr Fein:
Thank you, Jennifer. It's a pleasure to be with you.

Announcer:
In our discussion today, we will focus on the clinical profile of XARELTO®(rivaroxaban).

- XARELTO® is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (or AF)
- There are limited data on the relative effectiveness of XARELTO® and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well controlled
- XARELTO® is indicated for the treatment of deep vein thrombosis (or DVT)
- XARELTO® is indicated for the treatment of pulmonary embolism (or PE)
- XARELTO® is indicated for the reduction in the risk of recurrence of DVT and/or PE in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months
- XARELTO®is indicated for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery
- XARELTO® is indicated for the prophylaxis of venous thromboembolism (or VTE) and VTE-related death during hospitalization and post hospital discharge in adult patients admitted for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE, and not at high risk of bleeding

- XARELTO® is indicated, in combination with aspirin, to reduce the risk of major cardiovascular events (cardiovascular [or CV] death, myocardial infarction [or MI], and stroke) in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD)

Before we discuss XARELTO®, let's review the BOXED Warning and contraindications.

- XARELTO® carries a BOXED Warning. The first part notes that premature discontinuation of XARELTO® places patients at an increased risk of thrombotic events. This is based on a higher rate of thrombotic events in the XARELTO® arm compared with the warfarin arm following the discontinuation of XARELTO® and a nonbridged transition to warfarin at the end of the ROCKET AF trial. If anticoagulation with XARELTO® must be discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant
- The second part of the BOXED Warning pertains to epidural or spinal hematomas. These have occurred in patients treated with XARELTO® who are receiving neuraxial anesthesia or undergoing spinal puncture and may result in long-term or permanent paralysis
- Factors that can increase the risk of developing epidural or spinal hematomas in these patients include the use of indwelling epidural catheters, concomitant use of other drugs that affect hemostasis, a history of traumatic or repeated epidural or spinal punctures, or a history of spinal deformity or spinal surgery. Optimal timing between the administration of XARELTO® and neuraxial procedures is not known
- These patients should be monitored frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis
- Contraindications for XARELTO® include active pathological bleeding and severe hypersensitivity reaction to XARELTO®

Dr Caudle:
Absolutely, well we're excited. So, let's start, Dr Fein, with discussing 2 pivotal trials, EINSTEIN DVT and EINSTEIN PE. As I understand it, these trials examine XARELTO®as a treatment option for venous thromboembolism. Among numerous other subgroups, these studies included a subgroup population of patients with active cancer. So, can you tell us about the study design, Dr Fein?

Dr Fein:
Sure. EINSTEIN DVT and EINSTEIN PE were both randomized, open-label, event-driven, noninferiority studies that compared the safety and efficacy of XARELTO®with standard therapy enoxaparin, followed by vitamin K antagonist in patients with VTE. In EINSTEIN DVT, the definition of DVT was objectively confirmed proximal DVT without symptomatic PE. In EINSTEIN PE, the definition of PE was PE with or without DVT.

I'd like to point out that EINSTEIN PE is noteworthy because XARELTO®is the only DOAC with a dedicated PE trial. Treatment duration was 3, 6, or 12 months, as determined by the treating physician. Subjects were also monitored for an additional 30-day, post-study observation period. In both studies patients were randomized to receive XARELTO® 15 mg twice daily for 21 days, followed by XARELTO®20 mg once daily, or subcutaneous enoxaparin at a dose of 1 mg/kg twice daily for at least 5 days followed by a vitamin K antagonist to be initiated within 48 hours. For this group, the target INR was 2 to 3. The primary efficacy outcome was symptomatic, recurrent VTE defined as the composite of recurrent DVT, nonfatal PE, or fatal PE. And finally, the principal safety outcome was clinically relevant bleeding defined as the composite of major and clinically relevant non-major bleeding. I'll note that in the pooled analysis of both trials, approximately 8% of the intent-to-treat population had active cancer, either at baseline or diagnosed during the study, and around 18% of the randomized population had recent surgery or trauma.

Dr Caudle:
Excellent, Dr Fein. Thank you for describing the study designs. Now, can you share the findings from these trials, starting with EINSTEIN DVT?

Dr Fein:
Yes, sure. When it comes to efficacy, the key point is EINSTEIN DVT demonstrated that XARELTO®is noninferior to enoxaparin followed by vitamin K antagonist for the treatment of DVT. As a reminder, DVT was defined as acute, symptomatic proximal DVT without symptomatic PE. The primary efficacy outcome of recurrent VTE incidence rate was 2.1% for patients in the XARELTO®group versus 3% for patients in the standard therapy group by the end of the trial. Now, I'll share the safety results. First, as a reminder, the principal safety outcome was the composite of major and clinically relevant non-major bleeding. In this trial, rates of the composite of

major and clinically relevant non-major bleeding were similar between treatment groups with a rate of 8.1% for patients who received XARELTO®compared with 8.1% for patients who received standard therapy. I'll also mention that the major bleeding rate was 0.8% for the XARELTO®group versus 1.2% for patients in the enoxaparin and vitamin K antagonist group, which was a 35% relative risk reduction. Note that the rates of major bleeding were not adjusted for multiplicity.

Dr Caudle:
Great, and Dr Fein, now let's move on to EINSTEIN PE. What were the results of this trial?

Dr Fein:
The main takeaway from EINSTEIN PE is XARELTO®is noninferior to enoxaparin followed by vitamin K antagonist for the treatment of PE. As a reminder, in this study, PE was defined as acute, symptomatic PE, with or without DVT. The primary efficacy outcome of recurrent VTE incidence rate was 2.1% for patients in the XARELTO®group versus 1.8% for patients in the standard therapy group. The primary safety outcome was the composite of major and clinically relevant non-major bleeding, and the rates were similar between treatment groups, with a rate of 10.3% for patients receiving XARELTO® compared with 11.4% for patients receiving standard therapy. With regard to major bleeding only, the rates were 1.1% for patients receiving XARELTO® versus 2.2% for patients receiving standard therapy, which was a 51% relative risk reduction. Again, I will note these rates were not adjusted for multiplicity. In a pooled analysis of both trials, the major GI bleeding rates were 0.4% for the XARELTO® group versus 0.6% for the standard therapy group.

Dr Caudle:
So, Dr Fein, earlier you explained the EINSTEIN DVT and EINSTEIN PE trials that featured pooled subgroup analysis results in patients with active cancer. So, let's focus more specifically on this group. Can you share some details with us, Dr Fein?

Dr Fein:
Yes, I'd like to highlight that there were 655 patients enrolled in the EINSTEIN DVT and EINSTEIN PE studies who had active cancer. Of this number, 462 patients had known, active cancer at baseline, and 193 were diagnosed with cancer during the study. Active cancer at baseline was defined as a diagnosis of cancer that occurred within 6 months before enrollment, any treatment for cancer within the previous 6 months, or recurrent metastatic cancer. Active cancer during the study was defined as a new diagnosis of cancer, or recurrence of cancer after randomization. The key takeaway is that safety and efficacy results of the EINSTEIN DVT and EINSTEIN PE trials were generally consistent across patients with and without active cancer.

Now, let's look at the data. First, I'll mention that the following data in the subgroup analyses were not adjusted for multiplicity. Looking at the primary efficacy endpoint of recurrent VTE, the rates were 5% for patients who took XARELTO® versus 7% for patients who took standard therapy. For the principal safety endpoint of the composite of major and clinically relevant non-major bleeding, the rates were 14% for the XARELTO® group versus 16% for the standard therapy group. I'll point out that for major bleeding only, the rates were 2% and 5%, respectively.

Dr Caudle:
Thank you for sharing that data, Dr Fein, and as I understand it, there was actually another study that investigated the safety and efficacy of XARELTO® in treating VTE in patients with active cancer. Is that correct?

Dr Fein:
That's right, Dr Caudle. The study, called SELECT-D, was a randomized, open-label, multicenter pilot trial of 406 patients with active cancer, both solid tumor and hematologic malignancy. The patients presented with a primary, objectively confirmed VTE defined as either symptomatic, lower extremity, proximal DVT, symptomatic PE, or incidental PE. The study inclusion criteria were patients who were at least 18 years old, weighed at least 40 kg, had an ECOG score of 2 or less and had adequate hematologic, hepatic, and renal function. Patients were randomized to 2 groups. One group was treated with XARELTO® 15 mg twice daily for the first 3 weeks followed by 20 mg once daily for a total of 6 months, while the other group was treated with dalteparin 200 IU/kg once daily subcutaneous for the first 30 days followed by 150 IU/kg once daily for an additional 5 months.

In the SELECT-D study, the primary endpoint was VTE recurrence. The principal safety outcomes were major bleeding and clinically relevant non-major bleeding. In terms of the primary efficacy endpoint, the study results at 6 months showed a cumulative rate of VTE recurrence of 4% for patients treated with XARELTO® versus 11% for patients treated with dalteparin with a hazard ratio of 0.43 and a 95% confidence interval of 0.19 to 0.99. With regards to the principal safety outcomes, at 6 months the cumulative major bleed rate was similar between XARELTO® and dalteparin, while the cumulative rate of clinically relevant non-major bleeding was higher for XARELTO® versus dalteparin. Let's look at the numbers. The cumulative major bleed rate at 6 months was 6% for patients who received XARELTO®, compared with 4% for patients who received dalteparin. At the same point in time, a cumulative rate of clinically

relevant non-major bleeding was 13% XARELTO® versus 4% for dalteparin.

Announcer:
The following is additional Important Safety Information for XARELTO®

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including XARELTO®, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO®to warfarin in clinical trials in atrial fibrillation patients. If XARELTO®is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Risk of Bleeding:** XARELTO®increases the risk of bleeding and can cause serious or fatal bleeding. Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue in patients with active pathological hemorrhage.
  - An agent to reverse the anti-factor Xa activity of rivaroxaban is available. Because of high plasma protein binding, rivaroxaban is not dialyzable.
  - Concomitant use of other drugs that impair hemostasis increases risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, dual antiplatelet therapy, other antithrombotic agents, fibrinolytic therapy, NSAIDs, selective serotonin reuptake inhibitors (or SSRIs), and serotonin norepinephrine reuptake inhibitors (or SNRIs).
  - Risk of Hemorrhage in Acutely Ill Medical Patients at High Risk of Bleeding: Acutely ill medical patients with the following conditions are at increased risk of bleeding with the use of XARELTO®for primary VTE prophylaxis: history of bronchiectasis, pulmonary cavitation, or pulmonary hemorrhage; active cancer (ie, undergoing acute, in-hospital cancer treatment); active gastroduodenal ulcer or history of bleeding in the three months prior to treatment; or dual antiplatelet therapy. XARELTO®is not for use for primary VTE prophylaxis in these hospitalized, acutely ill medical patients at high risk of bleeding.
- **Spinal/Epidural Anesthesia or Puncture:** When neuraxial anesthesia (ie, spinal or epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis. To reduce the potential risk of bleeding associated with concurrent use of XARELTO®and epidural or spinal anesthesia and/or analgesia or spinal puncture, consider the pharmacokinetic profile of XARELTO®. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of XARELTO®is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. An indwelling epidural or intrathecal catheter should not be removed before at least 2 half-lives have elapsed (ie, 18 hours in young patients aged 20 to 45 years and 26 hours in elderly patients aged 60 to 76 years), after the last administration of XARELTO®. The next dose should not be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of XARELTO®for 24 hours. Monitor frequently to detect signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (for example, numbness, tingling, or weakness in lower limbs), or bowel and/or bladder dysfunction. Instruct patients to immediately report any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.
- **Use in Patients with Renal Impairment:**
  - **Nonvalvular Atrial Fibrillation:** Periodically assess renal function as clinically indicated (ie, more frequently in situations in which renal function may decline) and adjust therapy accordingly. Consider dose adjustment or discontinuation in patients who develop acute renal failure while on XARELTO®. Clinical efficacy and safety studies with XARELTO®did not enroll patients with CrCl <30 mL/min or end-stage renal disease (or ESRD) on dialysis.
  - **Treatment of Deep Vein Thrombosis (or DVT), Pulmonary Embolism (or PE), and Reduction in the Risk of Recurrence of DVT and of PE; for the Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery; for the Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding:** In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO®in these patients. Discontinue XARELTO®in patients who develop acute renal failure while on treatment.
  - **Reduction of Risk of Major Cardiovascular Events in Patients with Chronic CAD or PAD:** For patients with CrCl <15 mL/min, no

data are available, and limited data are available for patients with a CrCl of 15 to 30 mL/min. In patients with CrCl <30 mL/min, a dose of 2.5 mg of XARELTO®twice daily is expected to give an exposure similar to that in patients with a moderate renal impairment (CrCl 30 to <50 mL/min), whose efficacy and safety outcomes were similar to those with preserved renal function. Clinical efficacy and safety studies with XARELTO®did not enroll patients with end-stage renal disease (or ESRD) on dialysis.

- **Use in Patients with Hepatic Impairment:** No clinical data are available for patients with severe hepatic impairment. Avoid use in patients with moderate (or Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy, since drug exposure and bleeding risk may be increased.
- **Use with P-gp and Strong CYP3A Inhibitors or Inducers**: Avoid concomitant use of XARELTO®with known combined P-gp and strong CYP3A inhibitors or inducers.
- **Risk of Pregnancy-Related Hemorrhage:** In pregnant women, XARELTO®should be used only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO® dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO®cannot be monitored with standard laboratory testing. Promptly evaluate signs or symptoms suggesting blood loss (eg, a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).
- **Patients with Prosthetic Heart Valves:** Use of XARELTO® is not recommended in patients who have had transcatheter aortic valve replacement (TAVR), based on the results of the GALILEO study, which reported higher rates of death and bleeding in patients randomized to XARELTO® compared to those randomized to an antiplatelet regimen. Safety and efficacy of XARELTO® have not been studied in patients with other prosthetic heart valves or other valve procedures. Use of XARELTO® is not recommended in patients with prosthetic heart valves.
- **Acute PE in Hemodynamically Unstable Patients and/or Patients Who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of XARELTO®is not recommended acutely as an alternative to unfractionated heparin in patients with pulmonary embolism who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.
- **Increased Risk of Thrombosis in Patients with Antiphospholipid Syndrome:** Direct-acting oral anticoagulants (or DOACs), including XARELTO®, are not recommended in use in patients with triple-positive antiphospholipid syndrome (or APS). For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

DRUG INTERACTIONS

- Combined P-gp and strong CYP3A inhibitors increase exposure to rivaroxaban and may increase risk of bleeding.
- Combined P-gp and strong CYP3A inducers decrease exposure to rivaroxaban and may increase risk of thromboembolic events.
- XARELTO® should not be used in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A inhibitors (example, erythromycin) unless the potential benefit justifies the potential risk.
- Coadministration of enoxaparin, warfarin, aspirin, clopidogrel, and chronic NSAID use may increase risk of bleeding.
- Avoid concurrent use of XARELTO®with other anticoagulants due to increased bleeding risk, unless benefit outweighs risk. Promptly evaluate signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** The limited available data on XARELTO®in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Use XARELTO®with caution in pregnant patients because of the potential for pregnancy-related hemorrhage and/or emergent delivery. The anticoagulant effect of XARELTO®cannot be reliably monitored with standard laboratory testing. Consider the benefits and risks of XARELTO®for the mother and possible risks to the fetus when prescribing to a pregnant woman.
  - Fetal and/or Neonatal adverse reactions: Based on the pharmacologic activity of Factor Xa inhibitors and the potential to cross the placenta, bleeding may occur at any site in the fetus and/or neonate.
  - Labor or delivery: The risk of bleeding should be balanced with the risk of thrombotic events when considering use in this setting.
  - There are no adequate or well-controlled studies of XARELTO®in pregnant women, and dosing for pregnant women has not been established. Post-marketing experience is currently insufficient to determine a rivaroxaban-associated risk for major birth defects or miscarriage.
- **Lactation:** Rivaroxaban has been detected in human milk. There are insufficient data to determine the effects of rivaroxaban on the

breastfed child or on milk production. Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for XARELTO®and any potential adverse effects on the breastfed infant from XARELTO®or from the underlying maternal condition.

- **Females and Males of Reproductive Potential:** Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician. The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants, including XARELTO®, should be assessed in females of reproductive potential and those with abnormal uterine bleeding.
- **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

OVERDOSAGE

- Overdose of XARELTO®may lead to hemorrhage. Discontinue XARELTO®and initiate appropriate therapy if bleeding complications associated with overdosage occur. An agent to reverse the anti-factor Xa activity of rivaroxaban is available.

ADVERSE REACTIONS IN CLINICAL STUDIES

- Most common adverse reactions with XARELTO®were bleeding complications.

Please visit www.xareltohcp.com to read full Prescribing Information, including BOXED WARNINGS, for XARELTO®.

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Dr Caudle:
Now, unfortunately, we're just about out of time today. So, Dr Fein, what do you want our listeners to take away from this discussion?

Dr Fein:
I'd like to reiterate that in the EINSTEIN DVT and EINSTEIN PE trials, XARELTO® 15 mg twice daily for 21 days followed by 20 mg once daily was noninferior to enoxaparin followed by vitamin K antagonist, for the treatment of VTE. Additionally, the rates of the composite of major bleeding and clinically relevant non-major bleeding were similar in XARELTO® compared with patients receiving enoxaparin followed by vitamin K antagonist.

Dr Caudle:
Excellent. Is there anything else, Dr Fein? You know, what's your final takeaway?

Dr Fein:
My final takeaway, Jennifer, is that the clinical trial data exists that evaluated the use of XARELTO® to treat VTE in patients with active cancer. In the EINSTEIN DVT and EINSTEIN PE trials that I described, there was a pooled subgroup analysis of patients with active cancer. The safety and efficacy data were generally consistent between patients with active cancer and those without active cancer. In addition, I shared the results from the pilot study, SELECT-D, that examined the use of XARELTO® in patients with active cancer. The data show XARELTO® decreased VTE occurrences within 6 months compared with dalteparin. XARELTO® had similar rates of major bleeding, although a higher rate of clinically relevant non-major bleeding, compared with dalteparin.

Dr Caudle:
Well, with those takeaways in mind, I'd really like to thank my guest for taking us through the clinical trial data for VTE in patients with active cancer. Dr Fein, it was great speaking with you today.

Dr Fein:
It was my pleasure, Dr Caudle. Thank you for having me.

Announcer:
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