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Janssen Provides Update on Phase 3 ACIS Study in Patients with Metastatic Castration-Resistant Prostate Cancer Treated with ERLEADA® (apalutamide) and ZYTIGA® (abiraterone acetate) Plus Prednisone Combination

RARITAN, N.J., April 19, 2021 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today that regulatory submissions based on the Phase 3 ACIS study, which evaluated the combination of ERLEADA® (apalutamide) and ZYTIGA® (abiraterone acetate) plus prednisone in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC), will not be pursued. As [presented](#) at the American Society of Clinical Oncology’s Genitourinary (ASCO GU) Cancers Symposium in February 2021, the ACIS study met its primary endpoint of radiographic progression-free survival (rPFS); however, combination treatment did not show significant benefit over the active control ZYTIGA® plus prednisone in key secondary endpoints, including overall survival (OS).

“Safety results from ACIS were consistent with prior studies of ERLEADA and ZYTIGA plus prednisone, with no new safety signals observed. The study also generated valuable scientific outcomes and insights in subgroups of patients with luminal type in PAM50 test and tumors with average or high androgen receptor activity (molecular signatures of hormone sensitivity), which warrant further investigation,” said Kiran Patel, M.D., Vice President, Clinical Development, Solid Tumors, Janssen Research & Development, LLC. “These data will be important in informing

future programs in our pipeline, as we look to build upon our leadership and commitment in bringing transformational therapies to patients diagnosed with prostate cancer.”

About the ACIS Study

[ACIS](#) was a Phase 3 randomized, double-blind, placebo-controlled, multicenter clinical study evaluating the efficacy and safety of ERLEADA® and ZYTIGA® plus prednisone compared to placebo and ZYTIGA® plus prednisone in 982 patients with chemotherapy-naïve mCRPC who received ADT. The primary endpoint of the study was rPFS. Secondary endpoints of the study included OS, time to chronic opioid use, time to initiation of cytotoxic chemotherapy, and time to pain progression.

About Metastatic Castration-Resistant Prostate Cancer

Metastatic castration-resistant prostate cancer characterizes cancer that no longer responds to ADT and has spread to other parts of the body. The most common metastatic sites are bones, followed by lymph nodes, lungs, and liver.¹ Prostate cancer is the second most common type of cancer in men worldwide. More than one million men around the world are diagnosed with prostate cancer each year.²

About ERLEADA® (apalutamide)

ERLEADA® is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC) and for the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC).³ ERLEADA® received U.S. Food and Drug Administration (FDA) approval for nmCRPC on [February 14, 2018](#) and was approved for mCSPC on [September 17, 2019](#). To date, more than 25,000 patients worldwide have been treated with ERLEADA®. ERLEADA® is taken orally, once daily, with or without food.³ The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer include apalutamide (ERLEADA®) with continued androgen deprivation therapy**† as a Category 1 Preferred treatment option for patients with non-metastatic (M0) castration-resistant prostate cancer and a PSADT ≤10 months.⁴ The NCCN Clinical Practice Guidelines® also include apalutamide (ERLEADA®) with androgen deprivation**† as a Category 1 Preferred treatment option for patients with metastatic (M1) castration-naïve prostate cancer.†⁴ The American Urological Association (AUA) Guidelines for Castration-Resistant Prostate Cancer (CRPC) recommend clinicians offer apalutamide (ERLEADA®) with continued androgen deprivation therapy (ADT) as one of the treatment options for patients with nmCRPC at high risk for developing metastatic disease (Standard; Evidence Level Grade A)***.⁵ ERLEADA® is being further studied in two ongoing Phase 3 clinical trials.

For more information about ERLEADA®, visit www.ERLEADA.com.

*© National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed December 11, 2020. To view the most recent and complete version of the NCCN Guidelines®, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application, and disclaims any responsibility for their application or use in any way.

**Orchiectomy, LHRH agonist, or LHRH antagonist

†Use of an LHRH agonist plus a first-generation antiandrogen is an option for patients receiving ADT alone, but is not an option for patients receiving apalutamide.

‡The term "castration-naive" is used to define patients who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-naive" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of radiation therapy provided they have recovered testicular function.

***Standard: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade A or B evidence.

***Evidence Level: A designation indicating the certainty of the results as high, moderate, or low (A, B, or C, respectively) based on AUA nomenclature and methodology.

About ZYTIGA® (abiraterone acetate)

ZYTIGA® (abiraterone acetate) in combination with prednisone is indicated for the treatment of patients with mCRPC, approved by the U.S. FDA on [April 28, 2011](#) and by the European Commission on [September 7, 2011](#). Additionally, ZYTIGA® was approved for the treatment of high-risk mCSPC by the European Commission on [November 20, 2017](#) and by the U.S. FDA on [February 8, 2018](#).⁶ Since its first approval in the U.S. in 2011, ZYTIGA® has been approved in combination with prednisone or prednisolone, in more than 100 countries. More than 500,000 patients worldwide have been prescribed ZYTIGA®.

ERLEADA® IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS

Cerebrovascular and Ischemic Cardiovascular Events — In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 3% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 6 patients (0.5%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with current evidence of unstable angina, myocardial

infarction, or congestive heart failure within 6 months of randomization were excluded from the SPARTAN and TITAN studies.

Ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA[®]. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA[®] for Grade 3 and 4 events.

Fractures — In a randomized study (SPARTAN) of patients with nmCRPC, fractures occurred in 12% of patients treated with ERLEADA[®] and in 7% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 9% of patients treated with ERLEADA[®] and in 6% of patients treated with placebo. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

Falls — In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA[®] compared with 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Falls occurred in patients receiving ERLEADA[®] with increased frequency in the elderly. Evaluate patients for fall risk.

Seizure — In 2 randomized studies (SPARTAN and TITAN), 5 patients (0.4%) treated with ERLEADA[®] and 1 patient treated with placebo (0.1%) experienced a seizure. Permanently discontinue ERLEADA[®] in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA[®]. Advise patients of the risk of developing a seizure while receiving ERLEADA[®] and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

Embryo-Fetal Toxicity — The safety and efficacy of ERLEADA[®] have not been established in females. Based on its mechanism of action, ERLEADA[®] can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA[®] [see *Use in Specific Populations (8.1, 8.3)*].

ADVERSE REACTIONS

Adverse Reactions — The most common adverse reactions ($\geq 10\%$) that occurred more frequently in the ERLEADA[®]-treated patients ($\geq 2\%$ over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea and fracture.

Laboratory Abnormalities — All Grades (Grade 3-4)

- Hematology — In the TITAN study: white blood cell decreased ERLEADA® 27% (0.4%), placebo 19% (0.6%). In the SPARTAN study: anemia ERLEADA® 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA® 47% (0.3%), placebo 29% (0%); lymphopenia ERLEADA® 41% (2%), placebo 21% (2%)
- Chemistry — In the TITAN study: hypertriglyceridemia ERLEADA® 17% (3%), placebo 12% (2%). In the SPARTAN study: hypercholesterolemia ERLEADA® 76% (0.1%), placebo 46% (0%); hyperglycemia ERLEADA® 70% (2%), placebo 59% (1%); hypertriglyceridemia ERLEADA® 67% (2%), placebo 49% (0.8%); hyperkalemia ERLEADA® 32% (2%), placebo 22% (0.5%)

Rash — In 2 randomized studies, rash was most commonly described as macular or maculopapular. Adverse reactions of rash were 26% with ERLEADA® vs 8% with placebo. Grade 3 rashes (defined as covering >30% body surface area [BSA]) were reported with ERLEADA® treatment (6%) vs placebo (0.5%).

The onset of rash occurred at a median of 83 days. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA®.

Hypothyroidism — In 2 randomized studies, hypothyroidism was reported for 8% of patients treated with ERLEADA® and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA® and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA® — Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, reduce the ERLEADA® dose based on tolerability [*see Dosage and Administration (2.2)*].

Effect of ERLEADA® on Other Drugs — ERLEADA® is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA® with

medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA® with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA® and evaluate for loss of activity.

P-gp, BCRP or OATP1B1 Substrates — Apalutamide is a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. Concomitant use of ERLEADA® with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with ERLEADA® and evaluate for loss of activity if medication is continued.

Please see the full [Prescribing Information](#) for ERLEADA®.

ZYTIGA® IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hypokalemia, Fluid Retention, and Cardiovascular Adverse Reactions due to Mineralocorticoid Excess - ZYTIGA® may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition [see *Clinical Pharmacology (12.1)*]. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment.

Closely monitor patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia, or fluid retention, such as those with heart failure, recent myocardial infarction, cardiovascular disease, or ventricular arrhythmia. In post marketing experience, QT prolongation, and torsades de pointes have been observed in patients who develop hypokalemia while taking ZYTIGA®. The safety of ZYTIGA® in patients with left ventricular ejection fraction <50% or New York Heart Association (NYHA) Class III or IV heart failure (in COU-AA-301) or NYHA Class II to IV heart failure (in COU-AA-302 and LATITUDE) has not been established because these patients were excluded from these randomized clinical trials [see *Clinical Studies (14)*].

Adrenocortical Insufficiency - Adrenocortical insufficiency was reported in patients receiving ZYTIGA® in combination with prednisone, after an interruption of daily steroids and/or with

concurrent infection or stress. Monitor patients for symptoms and signs of adrenocortical insufficiency if prednisone is stopped or withdrawn, if the prednisone dose is reduced, or if the patient experiences unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA®. Perform appropriate tests, if clinically indicated, to confirm adrenocortical insufficiency. Increased dosages of corticosteroids may be used before, during, and after stressful situations [see *Warnings and Precautions (5.1)*].

Hepatotoxicity - In post marketing experience, there have been ZYTIGA®-associated severe hepatic toxicities, including fulminant hepatitis, acute liver failure, and deaths. Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA®, every two weeks for the first three months of treatment, and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced ZYTIGA® dose of 250 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment, and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the upper limit of normal (ULN) or the bilirubin rises above three times the ULN, interrupt ZYTIGA® treatment and closely monitor liver function. Re-treatment with ZYTIGA® at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN [see *Dosage and Administration (2.4)*].

Permanently discontinue ZYTIGA® for patients who develop a concurrent elevation of ALT greater than 3X ULN and total bilirubin greater than 2X ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.

The safety of ZYTIGA® re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

Increased Fractures and Mortality in Combination with Radium Ra 223 Dichloride

- ZYTIGA® plus prednisone/prednisolone is not recommended for use in combination with radium Ra 223 dichloride outside of clinical trials. Increased incidences of fractures (28.6% vs 11.4%) and deaths (38.5% vs 35.5%) have been observed in patients who received ZYTIGA® plus prednisone/prednisolone in combination with radium Ra 223 dichloride compared to patients who received placebo in combination with ZYTIGA® plus prednisone/prednisolone [see *Warnings and Precautions (5.4)*].

Embryo-Fetal Toxicity - The safety and efficacy of ZYTIGA® have not been established in females. Based on animal reproductive studies and mechanism of action, ZYTIGA® can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with ZYTIGA® and for 3 weeks after the last dose of ZYTIGA® [see *Use in Specific Populations (8.1, 8.3)*]. ZYTIGA® should not be handled by females who are or may become pregnant [see *How Supplied/Storage and Handling (16)*].

ADVERSE REACTIONS

Adverse Reactions - The most common adverse reactions ($\geq 10\%$) are fatigue, arthralgia, hypertension, nausea, edema, hypokalemia, hot flush, diarrhea, vomiting, upper respiratory tract infection, cough, and headache.

The most common laboratory abnormalities ($>20\%$) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, and hypokalemia.

Drug Interactions - Based on *in vitro* data, ZYTIGA® is a substrate of CYP3A4. In a drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during ZYTIGA® treatment. If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA® dosing frequency only during the co-administration period [see *Dosage and Administration (2.3)*]. In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

ZYTIGA® is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. Avoid co-administration with CYP2D6 substrates with a narrow therapeutic index. If alternative treatments cannot be used, consider a dose reduction of the CYP2D6 substrate drug. In a CYP2C8 drug interaction trial in healthy subjects, the AUC of pioglitazone, a CYP2C8 substrate, was increased by 46% when administered with a single dose of ZYTIGA®. Patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA®.

Use in Specific Populations -

- Females and Males of Reproductive Potential: Advise males with female partners of reproductive potential to use effective contraception.
- Do not use ZYTIGA® in patients with baseline severe hepatic impairment (Child-Pugh Class C).

Please read the full [Prescribing Information](#) and [Patient Information](#) for ZYTIGA®.

About the Janssen Pharmaceutical Companies of Johnson & Johnson

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular & Metabolism, Immunology, Infectious Diseases & Vaccines, Neuroscience, Oncology and Pulmonary Hypertension.

Learn more at www.janssen.com. Follow us at www.twitter.com/JanssenGlobal and www.twitter.com/JanssenUS. Janssen Research & Development, LLC is one of the Janssen Pharmaceutical Companies of Johnson & Johnson.

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Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding ERLEADA®(apalutamide) or ZYTIGA® (abiraterone acetate). 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, Janssen Biotech, Inc., 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 January 3, 2021, 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. None of 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.

¹ Cancer.org. Understanding advanced cancer, metastatic cancer, and bone metastasis. <https://www.cancer.org/treatment/understanding-your-diagnosis/advanced-cancer/what-is.html>. Accessed April 2021.

² World Health Organization. "Globocan 2012: Prostate Cancer: Incidence, Mortality and Prevalence Worldwide, 2012." <http://qco.iarc.fr/today/data/pdf/fact-sheets/cancers/cancer-fact-sheets-19.pdf>. Accessed April 2021.

³ ERLEADA[®] U.S. Prescribing Information, November 2020.

⁴ NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for Prostate Cancer V.3.2020. National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed December 2020.

⁵ American Urological Association. Castration-Resistant Prostate Cancer Guidelines. [http://www.auanet.org/guidelines/castration-resistant-prostate-cancer-\(2013-amended-2018\)](http://www.auanet.org/guidelines/castration-resistant-prostate-cancer-(2013-amended-2018)). Accessed April 2021.

⁶ ZYTIGA[®] U.S. Prescribing Information, October 2020.