

Media Inquiries:

Suzanne Frost
Phone: +1-416-317-0304

Brian Kenney
Phone: +1-215-620-0111

Investor Relations:

Christopher DelOrefice
Phone: +1-732-524-2955

Jennifer McIntyre
Phone: +1-732-524-3922

U.S. Medical Inquiries:
+1-800-526-7736

Janssen Announces Treatment with ERLEADA® (apalutamide) Significantly Improved Overall Survival in Patients with Metastatic Castration-Sensitive Prostate Cancer

Final analysis from Phase 3 TITAN study demonstrated ERLEADA® provided statistically significant overall survival benefit and consistent safety profile in patients with advanced prostate cancer, regardless of extent of disease

RARITAN, N.J., February 8, 2021 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today results from the final analysis of the Phase 3 TITAN study, which demonstrated the continued statistically significant benefit of the addition of ERLEADA® (apalutamide) to androgen deprivation therapy (ADT) in overall survival (OS) in patients with metastatic castration-sensitive prostate cancer (mCSPC), regardless of extent of disease, when compared to placebo plus ADT.¹ Results will be featured in an oral presentation at the American Society of Clinical Oncology’s Genitourinary (ASCO GU) Cancers Symposium, taking place virtually February 11-13, 2021 (Abstract #11; Rapid Abstract Session: Prostate Cancer, February 11, 3:30 PM-4:15 PM EST).

With nearly four years of median follow-up, data from the final analysis of the Phase 3 TITAN study confirmed that ERLEADA® plus ADT provided a statistically significant improvement in OS with a 35 percent reduction in risk of death versus ADT alone (HR 0.65; $p < 0.0001$).¹ The results were similar to the primary analysis of TITAN despite the subsequent crossover rate of almost 40

percent of the placebo-controlled group to the ERLEADA® arm. The improvement in OS increased to a 48 percent reduction in risk of death after adjusting for patients who crossed over (HR 0.52; p<0.0001).¹

“The TITAN final analysis further confirms that treatment with apalutamide can prolong overall survival and offer a clear long-term clinical benefit and established safety profile for patients with metastatic prostate cancer who are starting androgen deprivation therapy,” said Dr. Kim Chi, Medical Oncologist at BC Cancer - Vancouver and principal investigator of the TITAN study. “Based on these data, ADT alone should no longer be considered sufficient for patients with advanced, castration-sensitive disease.”

There was consistent benefit across other endpoints, including improved second progression-free survival (PFS2) (HR 0.62; p<0.0001) and delayed castration resistance (HR 0.34; p<0.0001). In addition, health-related quality of life (HRQoL), per total Functional Assessment of Cancer Therapy–Prostate (FACT-P), continued to be maintained with ERLEADA®. Safety and tolerability of ERLEADA® was consistent with previously reported studies.¹

“The TITAN final analysis data confirm the long-term clinical benefit and consistent safety profile of ERLEADA® plus ADT without a compromise in health-related quality of life,” said Mary Guckert, RN, MSN, Vice President, Development Leader, Prostate Cancer, Janssen Research & Development, LLC. “The results show the consistency and durability of ERLEADA® across advanced prostate cancer and underscore how ERLEADA® can fulfill a critical need.”

Initial results from the TITAN study [presented](#) at the 2019 American Society of Clinical Oncology Genitourinary Cancers Symposium (ASCO GU) and simultaneously [published](#) in *The New England Journal of Medicine* showed the addition of ERLEADA® (apalutamide) to ADT compared to placebo plus ADT significantly improved the dual primary endpoints of OS and radiographic progression-free survival (rPFS) in patients with mCSPC.²

To date, published results on ERLEADA® include data from more than 2,000 patients across Phase 3 clinical studies. ERLEADA® has shown a statistically significant improvement in OS with a consistent safety profile in both approved indications of mCSPC (TITAN) and non-metastatic castration-resistant prostate cancer or nmCRPC (SPARTAN).² ERLEADA® is currently approved in more than 74 countries, and labels are being updated globally to reflect these data from the TITAN final analysis.

About the TITAN Study²

TITAN ([NCT02489318](#)) is a Phase 3, randomized, placebo-controlled, double-blind study in patients with mCSPC. The study included 1,052 patients in 23 countries across 260 sites in North America, Latin America, South America, Europe, and Asia Pacific.³ Patients with mCSPC were randomized 1:1 and received either ERLEADA® (240 mg) plus ADT (n=524), or placebo plus ADT (n=527). The recruitment period for the study spanned from December 2015 to July 2017.² The study included patients with mCSPC with both low- and high-volume disease, those who were newly diagnosed, and those who had received prior definitive local therapy or prior treatment with up to six cycles of docetaxel for mCSPC.²

An Independent Data-Monitoring Committee was commissioned by the sponsor to monitor safety and efficacy.³ Dual primary endpoints of the study were OS and rPFS.¹ Secondary endpoints included time to cytotoxic chemotherapy, time to pain progression, time to chronic opioid use, and time to skeletal-related events.³ Exploratory endpoints included time to prostate specific antigen (PSA) progression, PFS2 and time to symptomatic progression.³ For additional study information, visit [ClinicalTrials.gov](#).

About Metastatic Castration-Sensitive Prostate Cancer

Metastatic castration-sensitive prostate cancer, also known as metastatic hormone-sensitive prostate cancer (mHSPC), refers to prostate cancer that still responds to hormonal therapy and has spread beyond the prostate to other parts of the body.⁴

About ERLEADA® (apalutamide)

ERLEADA® is an androgen receptor (AR) inhibitor indicated for the treatment of patients with nmCRPC and for the treatment of patients with mCSPC. 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](#).² To date, more than 10,000 patients worldwide have been treated with ERLEADA®. ERLEADA® is taken orally, once daily, with or without food.² 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 PSA doubling time (PSADT) ≤10 months.⁵ The NCCN 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)^{***}.⁶ ERLEADA® is being studied in five Phase 3 registrational 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.

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[®].

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 part 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). 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 29, 2019, 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 of Johnson & Johnson nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

¹ Chi, K. Final Analysis Results From TITAN: A Phase 3 Study of Apalutamide (APA) vs Placebo (PBO) in Patients (pts) With Metastatic Castration-Sensitive Prostate Cancer (mCSPC) Receiving Androgen Deprivation Therapy (ADT). ASCO GU 2021 Oral Presentation.

² ERLEADA® Prescribing Information, September 17, 2019.

³ Chi, K. Apalutamide for Metastatic, Castration Sensitive Prostate Cancer. *New England Journal of Medicine*. Accessed February 2021.

⁴ American Society of Clinical Oncology. ASCO Answers: Prostate Cancer (2018).

http://www.cancer.net/sites/cancer.net/files/asco_answers_guide_prostate.pdf. Accessed February 2021.

⁵ 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.

⁶ 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 February 2020.